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VOLUME 238 MARCH 25, 1948 NUMBER 13

The Treatment of Arterial Embolism . . . 421
Richard Warren and Robert R. Linton

Idiopathic Hyperlipemia 429
Winthrop C. Hopgood

Streptomycin Treatment in Acute Brucellosis 431
Calderon Howe and James T. Heyl

The Value of a Special Auricular Lead and of Carotid-Sinus Pressure in the Electrocardiographic Diagnosis of Tachycardias and Other Disorders of the Heart Beat . . 434
Laurence B. Ellis, Leslie W. Lannan and James M. Faulkner

Massachusetts Medical Society 451

Massachusetts Department of Public Health . 451

Correspondence 452

Medical Progress: Diabetes (To be concluded) . 437
Elliott P. Joslin, Leo P. Krall, C. C. Bailey, Howard F. Root, Priscilla White and Alexander Marble

Case Records of the Massachusetts General Hospital 443

Editorials:

Threatened Curtailment of State Laboratory Services 449

WHO 449

Now I Lay Me — 450

Books Received 453

Notices 455

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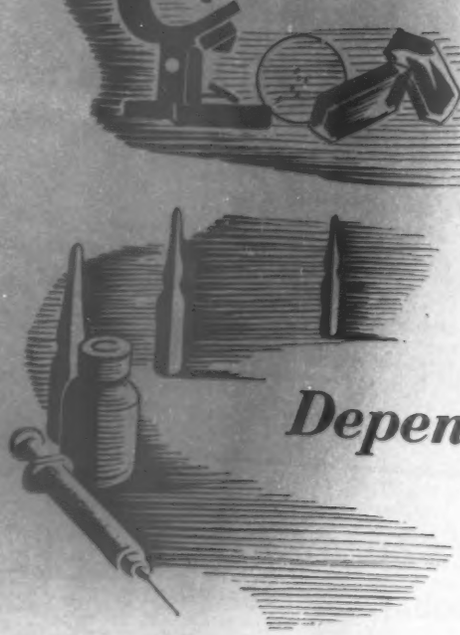

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Volume 238 MARCH 25, 1948 Number 13

THE TREATMENT OF ARTERIAL EMBOLISM*

RICHARD WARREN, M.D.,† AND ROBERT R. LINTON, M.D.‡

BOSTON

ALTHOUGH doctors since the time of William Harvey may have had some conception of the pathologic physiology of thrombosis and embolism and although John Hunter,[1] in 1794, reported intravascular coagulation occurring during life, it was not until the time of Virchow[2] (1845) that arterial embolism was clearly described and until later in the century (1895) that the operation of embolectomy was first attempted by Ssabanejeff[3] in Russia. From then until 1911 embolectomy was performed a dozen or more times without success before Labey[4] first successfully removed an embolus from the femoral artery. A short time later Key,[5, 6] in Sweden, was also successful. During the next ten years, Key demonstrated the possibilities of the operation and expanded its use to the utmost in the medical system of Sweden. In ten years Swedish authors were able to report results in 382 cases of embolectomy for arterial embolism of the extremities.[7] At that time numerous small series were first reported from clinics in this country,[8–14] so that by the year 1932 the medical profession had been able to form some preliminary conclusions regarding the place of surgery in this condition.

These conclusions were that arterial emboli usually occur in patients with heart disease who are in middle age, that the most common site of lodgment is a bifurcation of a major artery, usually the bifurcation of the femoral vessels, and that removal of the embolus before ten hours from onset have elapsed often, but not always, saves the limb. Simultaneously with the acceptance of these general conclusions a step forward was taken in the conservative treatment of acute arterial occlusion. Intermittent positive and negative pressure was introduced by Herrmann and Reid,[15] and intermittent venous occlusion by Collens and Wilensky.[16] The oscillating bed has been a more modern improvement on this principle. The role of arterial and arteriolar spasm in acute occlusion and the possibility of relief by interruption of the sympathetic pathways, either surgically or otherwise, were becoming familiar in 1934.[17, 18] It was at the same time that the purification of heparin by Charles and Scott[19] to the point where it could be used therapeutically furnished a logical means of preventing the blockage of vital collateral circulation by the distal propagating thrombus that follows embolism.[20, 21] With these new weapons available a few authors have suggested that surgery in the treatment of arterial embolism should be, if not abandoned, at least relegated to a position secondary to the newer conservative methods.[15, 22, 23]

It was with these considerations in mind that we undertook to examine our own experience with arterial emboli to determine what place, if any, the operation of embolectomy should play in the therapy of this condition. We have carefully studied the records of 98 patients who suffered 172 arterial emboli during the period 1937 to 1946.

When we first examined the record we discovered that although the operation is well known and the condition is presumably common, embolectomy was performed only forty-three times in twenty-two years.[8, 11] This is a frequency of two operations per year in a hospital to which an average of 6842 patients are admitted and in which an average of 4637 operations are performed each year. That this infrequency is not confined to our hospital, however, is testified to by the small size of most individual series reported and by the fact that McClure and Harkins[24] found only 690 cases reported in the world literature in thirty-three years.

For a better consideration of the disease as a whole, the first section of this paper is devoted to statistical matters concerning all emboli wherever lodged, the second section being confined to the limb emboli for which more specific means of therapy are available.

GENERAL CONSIDERATIONS

Sites of Embolism

Figure 1 shows the sites of lodgment of the 172 emboli in the series. Of the total group 110 cases, or 63.9 per cent, occurred in the limbs. Table 1

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presents a comparison of the sites of peripheral emboli with other figures from the literature.

There is a constant statistical trend of incidence at the various sites regardless of the source of the figures. It must be emphasized that the data presented in Figure 1, which shows the frequency of the diagnosis of emboli to the brain, spleen, kidney and skin, were obtained from clinical statistics as listed in a diagnosis file. In view of the fact that these

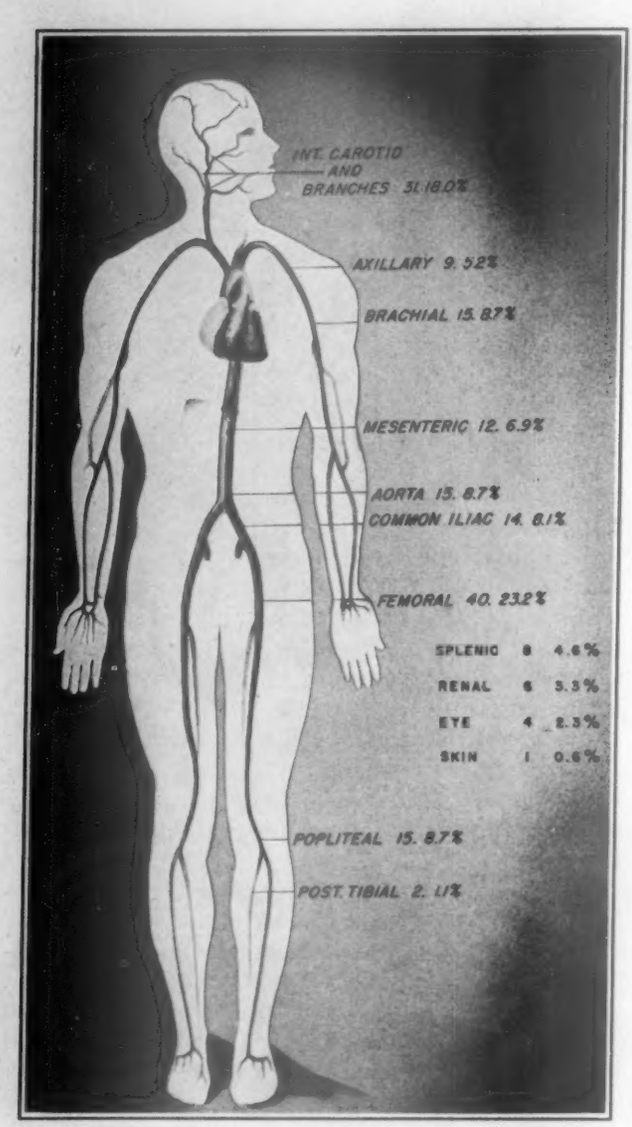

FIGURE 1. *Sites of Lodgment of 172 Arterial Emboli.*

diagnoses are often the least important of a group of major primary ones in a given case, it is probable that they are frequently not mentioned in the final list. It is certain, therefore, that the incidence of these particular emboli as listed is lower than the actual incidence. An examination of the diagnoses in the autopsy file during the same period shows an incidence of emboli to brain, spleen and kidney considerably higher than that derived from the clinical study (Table 2). Like the clinical statistics, however, these figures cannot be considered representative of the whole picture, because they obviously do not include surgical and nonlethal emboli. In Bull's[25] material also the incidence of emboli to internal organs (such as the spleen and kidneys) at autopsy was higher than that in clinical figures.

The possible sources of arterial emboli have been listed by Agar[26] as pulmonary veins, mural thrombi in the heart, mitral-valve vegetations, atheromatous plaques in the aorta and, very rarely, the systemic veins or the right side of the heart through a patent interventricular septum or foramen ovale as originally described by Cohnheim.[27] To these Gross,[28] in a report on the occurrence of arterial emboli in children, has added thrombus from a closing ductus arteriosus. The embolus usually consists of a thrombus that has broken away from one of the sites described above. The possibility that emboli made up of fragments of tumor invade the large arteries or, more logically, the pulmonary veins, become detached and lodge in the periphery has long been postulated. That this actually occurs is shown in the interesting case reported by Groth[29] in which a sarcoma of the right hip traveled to the lung as a venous embolism and from there at a later date became an embolism to the left femoral artery. From here it and its very long propagating thrombus were removed surgically, and the leg was saved. Pathological examination of the amputated right leg, a specimen of tissue from the lung and the embolectomy specimen from the left femoral artery showed identical tumors. Emboli consisting of retained metallic projectiles have also been reported.[30]

The most common source of emboli is generally considered to be intracardiac. Danzis[9] states that 60 per cent are due to cardiac disease. Koucky et al.[31] state that 13 of their 25 patients had auricular fibrillation. Generally, the elucidation of etiologic factors has not been clear from the data presented. This has not been true in our study (Table 3), which shows that in 87 of the 98 patients, or 88.7 per cent, a clinical diagnosis could be made that gave presumptive evidence of a source of embolism within the heart (Fig. 2). It is our impression from these observations that the presence or absence of a coronary occlusion, auricular fibrillation or bacterial endocarditis should offer a powerful argument for or against the diagnosis of arterial embolism, particularly since of the 11 patients with embolism from "undetermined" cause the records of 9 are not adequate to exclude any one or all of these etiologic factors. In only 2 patients did all the causes seem to be entirely excluded.

Since auricular fibrillation with presumably auricular thrombosis was the major cause of embolism it is of some interest to examine the causes of the fibrillation in these 64 cases (Table 4). It can be seen that rheumatic heart disease was responsible for about

two thirds of the cases of fibrillation and arteriosclerotic heart disease for the remainder. Although fibrillation due to thyrotoxicosis has been reported as causing emboli,[32] no such cases occurred in this series.

It has often been taught that drugs that restore a fibrillating auricle to normal rhythm may precipitate emboli. It is of interest that this sequence of events could not be established in any of our patients.

Sex and Age

The sex and age were determined in 97 of the 98 patients. There were 46 female and 51 male patients. The average age was fifty-two years, with extremes of twelve and seventy-seven years. The ages by decades are demonstrated in Figure 3. The youngest patient suffered a cerebral embolism from a subacute bacterial endocarditis superimposed on a congenital deformity described as the tetralogy of Fallot. The next youngest patient was twenty years of age, the embolism being caused by an auricular thrombus due to auricular fibrillation. The basic disease was rheumatic heart disease with mitral stenosis. It is of some interest to consider the average age of the groups when they are divided according to etiology. The average age of the 15 patients with mural thrombi due to myocardial infarction was fifty-seven and two-thirds years, which is, as might be expected, slightly above the average. The average age of the 7 patients whose emboli were caused by bacterial endocarditis was forty-five and a half years, or slightly below the average. The average age of the 64 patients who suffered from emboli originating in auricular thrombi on the basis of auricular fibrillation was fifty-two years, or exactly at the over-all average. This group contained both the oldest and the next to the youngest patients. Table 4, which shows the basic heart disease in the patients with auricular fibrillation and demonstrates that only about two thirds of them suffered from rheumatic heart disease (most of the remainder having arteriosclerotic heart disease), explains the broad range of age in these patients.

The statistics from this study are similar to those reported by Petitpierre[21] in his group of 129 cases of embolectomy. He found the peak incidence in the fifth and sixth decades. There was a slight preponderance of female over male patients (a ratio of 63:51).

Differential Diagnosis

In unoperated and unautopsied patients the diagnosis of embolism is always presumptive. It is for this reason that most series that have been published deal solely with operative cases. Conditions that may be confused with emboli are chiefly two in number: arterial thrombosis and acute thrombophlebitis of the deep veins of an extremity. The former is much more frequent than the latter. In

TABLE 1. *Sites of Peripheral Emboli, including Aortic Bifurcation.*

SITE	MASSACHUSETTS GENERAL HOSPITAL CASES	CASES REPORTED BY KEY[1,4]	CASES REPORTED BY PETITPIERRE[21]	CASES REPORTED BY DANZIS[3]
Subclavian artery	0	0	1 (0.7%)	2 (1.5%)
Axillary artery	9 (8.2%)	45 (11.8%)	10 (7.7%)	7 (5.4%)
Brachial artery	15 (13.6%)		10 (7.7%)	19 (14.7%)
Radial and ulnar arteries	0	1 (0.3%)	2 (1.4%)	1 (0.7%)
Aorta	15 (13.6%)	17 (4.5%)	12 (9.3%)	11 (8.5%)
Iliac artery	14 (12.7%)	66 (17.2%)	26 (20.1%)	23 (17.8%)
Femoral artery	40 (36.6%)	208 (54.4%)	57 (44.5%)	52 (40.3%)
Popliteal artery	15 (13.6%)	43 (11.3%)	10 (7.7%)	12 (9.2%)
Posterior tibial artery	2 (1.8%)	2 (0.5%)	1 (0.7%)	2 (1.5%)
Totals	110	382	129	129

TABLE 2. *Sites of Embolism in 74 Cases in 11,000 Autopsies.*

SITE	NO. OF CASES
Cerebral artery	33
Central retinal artery	1
Internal carotid artery	1
Vertebral artery	1
Coronary artery	8
Pancreatic artery	1
Mesenteric artery	12
Renal artery	7
Splenic artery	4
Brachial artery	1
Aorta	5
Iliac artery	8
Femoral artery	3
Popliteal artery	3
"Leg"	2
"Fingers and toes"	1
Total	91

TABLE 3. *Causes of Arterial Embolism in 98 Patients.*

CAUSE	NO. OF CASES
Auricular fibrillation	64
Myocardial infarction	15
Subacute bacterial endocarditis	7
Auricular fibrillation and myocardial infarction	1
Undetermined	11
Total	98

acute arterial occlusion in a patient with arteriosclerosis, thrombosis, as pointed out by Linton,[11] can never be ruled out until direct observation of the vessel is made. In spite of the fact that the lodgment of an embolus is a severe vascular accident and according to most descriptions is accompanied by a sudden onset of severe pain, only 69 per cent of our patients experienced a sudden onset of emboli and only 55.8 per cent suffering from limb emboli had severe pain.

The site of the vascular occlusion is of some help in the differential diagnosis of the thrombosis.

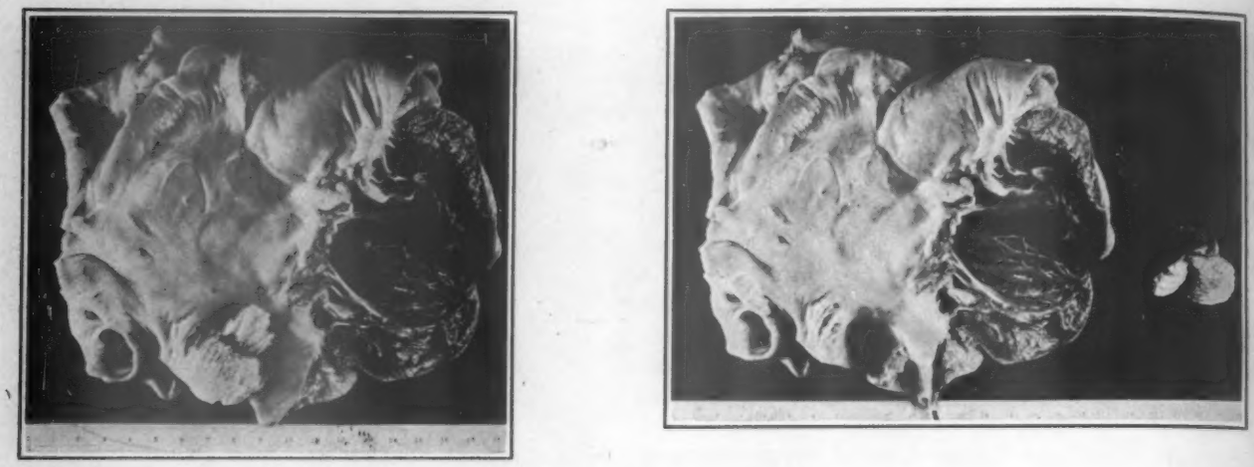

FIGURE 2. *Auricular Thrombosis.*

Photograph of the heart obtained at autopsy in a fifty-four-year-old man who, having had auricular fibrillation for eleven years due to rheumatic heart disease, entered the hospital in heart failure, from which he died eleven days later. Two episodes of arterial embolism occurred before death, one to the right popliteal artery one month before admission, and the other to the abdominal aorta two days before death.

TABLE 4. *Causes of Auricular Fibrillation in 64 Patients Suffering Arterial Emboli from Auricular Thrombi.*

CAUSE	NO. OF CASES
Rheumatic heart disease	41
Arteriosclerotic and hypertensive heart disease	17
Pick's disease (polyserositis)	1
Unknown	5
Total	64

Table 5 shows the location of 149 cases clinically diagnosed as arterial thromboses, excluding those of the coronary vessels, in 147 patients during the same period under study. The higher incidence of popliteal and mesenteric thrombosis in this table is of some significance in differentiating thrombosis from embolism. It has only a statistical value, however, since both popliteal embolism and acute femoral thrombosis occur in a significant number of cases. The clinical demonstration, or lack of it, of a source of embolism must chiefly be relied upon. As pointed out below, however, attempts to make this differential diagnosis in difficult cases must not be persisted in too long. In doubtful cases it is better to err on the side of embolism, since therapy cannot wait upon academic proof.

The other condition that in rare but significant cases must be differentiated from embolism and from thrombosis as well is acute thrombophlebitis. As shown by Leriche and Kunlin,[17] Danzis,[9] Edwards,[33] Ochsner and DeBakey[34] and Fontaine and Forster,[35] massive blockage of the deep venous spaces of the leg may throw the arteries into such a degree of spasm that the palpable pulses can disappear. A suggestive line of skin demarcation can ensue and even lead to gangrene. Careful inspection of the limb for venous engorgement, lack of muscular paralysis and anesthesia and the use of an oscillometer or aneroid sphygmomanometer to detect the presence or absence of oscillation in the calf will make this differential diagnosis.

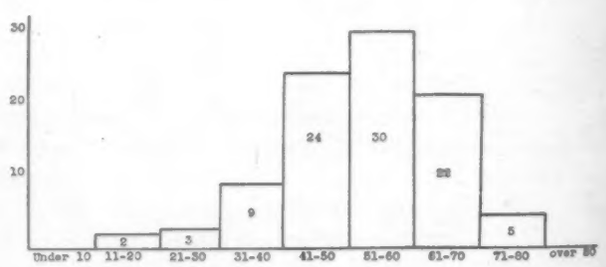

FIGURE 3. *Incidence of Arterial Emboli according to Decades.*

Embolism to Limb Arteries

The object of this section is to discuss the prognosis without treatment of arterial emboli to the major limb arteries, the types of treatment available and the results of these methods in the hands of others and in our own. Table 6 gives a composite view of our results.

Results with No Treatment

It is generally conceded that arterial emboli to the upper limb that are untreated carry a better prognosis than those to the lower limb.[6, 12] The correct figures are difficult to obtain, particularly from recent studies, since in all cases at present some form of treatment is used. In our cases 110 emboli involved the extremities. Thirteen of these are not suitable for evaluation of treatment since the patients died too soon after admission. Of the remaining 97, 38 received no treatment, and only 21 (55.2 per cent) of limbs were saved. To evaluate fairly these figures, it must be stated that the reason these patients received no treatment was that they were admitted to the hospital so late that the fate of the limb had already been decided by the time they were first observed. No treatment, therefore, was necessary other than amputation if the result had been unfavorable or mere treatment of the basic cardiac disease if it had been favorable.

Table 5. *Sites of Acute Arterial Thromboses in 147 Patients (Coronary Thrombosis Excluded).*

Site	No. of Cases	Percentage
Cerebral artery	4	2.7
"Eye"	2	1.3
Vertebral artery	1	0.6
Mesenteric artery	28	18.9
Subclavian artery	1	0.6
Axillary artery	2	1.3
Brachial artery	4	2.7
Aorta	4	2.7
Iliac artery	2	1.3
Femoral artery	20	13.5
Popliteal artery	41	27.6
Posterior tibial artery	21	14.1
"Leg"	15	10.8
"Foot"	3	2.0
Total	148	

The rate of limbs saved without treatment seems high. One might say that this figure compares favorably with some statistics on operative results. An important consideration is that in the majority of patients who received no treatment the emboli were to the upper extremity, where the prognosis is known to be better than that in the lower limb. In 23 analyzable cases affecting the upper limb 14 received no treatment; in these cases all limbs were saved. In the lower limb among 24 analyzable cases with no treatment limbs were saved in only 7, and were lost in 17. Thus, the 55.2 per cent salvage for all limbs under no treatment is reduced to 29.1 per cent if only the lower limbs are considered.

Results with Conservative Treatment

Conservative treatment was available during the whole ten-year period. In 1937 and 1938 the principal conservative methods used were papaverine,[22] paravertebral novocain block[17] and the Pavaex boot for the administration of intermittent suction and pressure.[15] After 1939 the Pavaex boot gave place largely to intermittent venous occlusion and the oscillating bed. The use of the other conservative methods was continued.

Our results are drawn from 38 analyzable cases in which 25 limbs, or 65.8 per cent, were saved by these methods. When the results in cases involving the lower extremity are examined in the same manner, one finds 20 of 32, or 62.5 per cent, limbs saved. Therefore, this form of treatment stands up well under the more rigid examination.

An attempt to evaluate individually the various available forms of nonoperative treatment from our records was fruitless. Most often they were used in combination. The reputation of none of the methods is unbesmirched by the loss of one or more limbs during or after its use. Heparin, for instance,

Table 6. *Results of Various Forms of Treatment, according to Site, in 110 Emboli of Peripheral Arteries.*

Site	Limbs with Tissue Saved			Limbs with Tissue Lost			Limbs Not Analyzable		Totals
	Operation	Conservative Treatment	No Treatment	Operation	Conservative Treatment	No Treatment	Operation	No Treatment	
Axillary artery	2	2	5	0	0	0	0	0	9
Brachial artery	1	3	9	0	1	0	0	1	15
Aorta	2	2	1	1	0	5	1	3	15
Iliac artery	0	1	2	1	2	3	2	3	14
Femoral artery	13	9	2	1	5	7	1	2	40
Popliteal artery	0	8	0	0	5	2	0	0	15
Tibial artery	0	0	2	0	0	0	0	0	2
Totals*	18	25	21	3	13	17	4	9	110

*The total number of cases in which no treatment was given was 47, of which 38 were analyzable and in which 21 limbs (55.2 per cent) were saved. The total number of cases in which conservative treatment was given was 38, of which 38 were analyzable and in which 25 limbs (65.8 per cent) were saved. Operation was performed in 25 cases, of which 21 were analyzable and in which 18 limbs (85.7 per cent) were saved.

was used in 9 cases. The limbs were saved in 5 and lost in 4; in some of the former the drug was employed as a last resort, and in some of the latter the limbs might have been saved without it. On theoretical grounds the use of these adjuncts in patients on whom surgery is impossible or who are waiting for surgery or have had unsuccessful surgery seems logical. Paravertebral block relaxes spasm and opens collateral vessels, and heparin should prevent the distal propagating thrombus. Although there is conflicting evidence concerning the value of intermittent venous occlusion[36, 37] and passive vascular exercises our clinical impression has been that these are the most valuable adjuncts of all.

The conservative weapon that we have found least useful has been papaverine. Clinical observations have revealed little benefit from this drug other than a certain amount of pain relief. The experimental work of Abramson[38] and others has shown that this drug produces little improvement in the vascular responses in the limbs.

Results of Surgical Treatment

A review of the literature reveals that the overall results of embolectomy are disappointing if one wishes to set up as a goal the ideal of 100 per cent survival of limbs and patients. There is as yet little that can be done about patients who die of heart failure or cerebral embolism. We should, however, be able to save 100 per cent of limbs. Since the muscles of a limb can survive complete lack of oxygen for only a limited time — perhaps six to ten hours[39] — the results in patients who have been operated upon within a very few hours of onset are far better than in those having later operations. The value of statistics must be criticized with this factor in mind.

Table 7 shows the results of surgical treatment gleaned from several series in the literature. The favorable results range between 25 and 50 per cent in the larger series and considerably higher in two smaller series, if one does not exclude patients whose limbs were saved but who died in the hospital of primary heart disease. Some authors argue that surgery in patients who are soon to die of their primary disease is not worth while. There is no question, however, that the prevention of gangrene can spare the patient much suffering. In addition, it is not always possible at a given point during the acute stage of the disease to separate the doomed patients from those destined to survive.

TABLE 7. *Results of Surgical Treatment of Embolism.*

SOURCE OF DATA	DATE	TOTAL NO. OF CASES	ANALYZABLE CASES	TOTAL LIMBS SAVED	UPPER EXTREMITIES		LOWER EXTREMITIES		MORTALITY	REMARKS
				PERCENTAGE	NO. INVOLVED	PERCENTAGE SAVED	NO. INVOLVED	PERCENTAGE SAVED	PERCENTAGE	
Petitpierre[11]	1928	129	126	44.4*	24	45.8	105	23.8	50.0	Prognosis for salvage of limb considered good up to 10 hr.
Danzis[9]	1933	129†	103	47.5	—	58.0	—	28.8	55.8	Rate of limb salvage: 1-4 hr., 62%; 4-8 hr., 50%; 8-12 hr., 25%; 12-24 hr., 21%.
Pearse[13]	1933	282	—	30.0	—	43.5	—	27.5	52.0	Rate of limb salvage: under 10 hr., 40%; 11-20 hr., 14%; 21-30 hr., 8%.
Strömbeck[43]	1936	327	120	50.0	24	62.5	96	47.7	63.0	—
Key[41]	1936	48	—	54.1	4	100.0	44	50.0	39.5	Prognosis for salvage of limb considered good up to 10 hr.; after 24 hr. operation regarded as of "no use."
Lund[33]	1937	27	—	57.7	—	85.7	—	47.4	44.4	—
Reynolds and Jirka[42]	1944	16	13	87.5	—	—	—	—	75.0	Under 18 hr. all limbs saved
Massachusetts General Hospital	1937–1941	25	21	85.7	3	100.0	18	83.4	28.6	Under 11 hr. all limbs but 1 saved

*Figure not clear since circulation is listed as restored in 5 cases in which gangrene developed.
†Many patients the same as those of Petitpierre, but series not identical.

The following analysis of our surgical results is given. Twenty-one patients were operated upon for removal of emboli. Twenty-five operations were performed, 4 patients having two operations each, the second operation being done for occurrence of emboli either at a new site or at the old one.

Four of these emboli were in 3 patients who died so soon that the effect of operation on the limbs could not be determined. Of 21 analyzable limbs, 18 or 85.7 per cent, survived.

In the 3 cases in which the limbs were lost there was technical difficulty in removing the embolus in 2 cases because the clot was adherent to the artery.

There was difficulty in the other case because of inability to remove all the clot satisfactorily from an embolus at the aortic bifurcation through bilateral femoral incisions. The elapsed time from onset to embolectomy in the former 2 cases was nine and a half and seventeen hours, and in the latter three hours.

Mortality and Causes of Death

A total of 38 of the 98 patients died in the hospital, a mortality of 38.7 per cent (Table 8). All patients died of cardiovascular disease. The surgically treated patients showed a mortality of 28.6 per cent, the rate for the nonsurgically treated cases, therefore, being somewhat above the average. The mortality figures from other clinics where the emboli of major peripheral arteries are treated surgically are higher (Petitpierre,[21] 50 per cent, Nystrom,[7] 60 per cent, and Strömbeck,[40] 63 per cent).

We consider these results to demonstrate that surgery itself is usually not harmful. Exceptions to this statement may be that operation on the abdominal aorta, since it cannot be done under local anesthesia, is poorly tolerated by the desperately ill patient; that operation on the popliteal artery is technically so difficult to perform without injury to collateral vessels or constriction of the small bifurcation of the artery by the suture line that conservative treatment is regarded as the one of choice; and that in a patient with very advanced peripheral arteriosclerosis the likelihood of thrombosis at the arteriotomy suture line after embolectomy is great, since the neat atraumatic suturing of an irregularly calcified arterial wall may be impossible — in such a patient, therefore, surgery may be decided against on this basis. The 1 death in this series that could possibly be attributed to surgery occurred on the operating table in collapse of a very sick forty-year-old woman with rheumatic heart disease who had just had an embolus removed from the aorta. Surgery should not be condemned on the basis of such a case, however, since 2 patients in the group died under similar circumstances on the way to the operating room before any anesthesia had been given or incision made.

Time Factor in the Treatment of Embolism

The speed with which the patient is brought to the surgeon after the embolism has struck is known to be of the utmost importance. Key considered ten hours to be the period chosen as a dividing line between favorable and unfavorable results. Table 7 shows that in the experience of others this figure has remained the best approximation available. Experimental evidence also suggests that it is accurate.[39]

The average elapsed time from onset to surgery in the 16 patients whose limbs survived was eight and three-quarter hours. The longest elapsed time was eleven hours, except in a case in which a femoral embolism was removed sixty hours after onset; in this patient a pregangrenous state of two toes was converted into a viable foot by the procedure, pulses that had previously been absent actually returning to the foot. Although successful late embolectomy has been reported by Hopkins[22] and others, it is the exception rather than the rule that an embolus that has been lodged for this length of time is not so adherent that it cannot be removed.

TABLE 8. *Hospital Mortality and Cause of Death in 98 Patients with Arterial Embolism.*

CAUSE OF DEATH	SURGICAL CASES	NONSURGICAL CASES	TOTAL
Cerebral embolism	—	14	14
Cardiac failure	5	5	10
Mesenteric embolism	1	6	7
Myocardial infarction	—	4	4
Pulmonary embolism	—	1	1
Subacute bacterial endocarditis	—	—	—
Unknown	—	1	1
Totals	6 (28.6%)*	32 (41.5%)†	38 (38.7%)

*Of 21 cases.
†Of 77 cases.

Surgery should not necessarily be abandoned in peripheral embolism because a temporal "deadline" has been passed. Much, of course, depends on the appearance of the limb. If actual gangrene has set in, as may happen within two days, embolectomy is not to be considered. If, however, there is calf paralysis, foot anesthesia and marked vasospasm with a line of demarcation that is suggestive only, embolectomy followed by conservative supportive measures should be performed.

Late Results

When a patient presents himself with an acute arterial occlusion, efforts are primarily directed at saving the limb. It has been shown[48] that even if the tissues of the limb survive complete arterial occlusion there is a likelihood of future difficulty with proper mechanics of the member if the main arterial trunk is allowed to remain obstructed. Strömbeck[40] has left a very complete report on the follow-up examination of a large number of patients. Of the 327 patients, 61 were discharged from the hospital after successful peripheral-artery embolectomy. Of these 61, three fourths lived for one year, half lived for three years, a third lived for five years, and one eighth lived for ten years. At the time of the report 41 patients had died. The cause of death in 20 of these was heart failure; in 12 death was caused by hemiplegia presumably due to embolism to the brain. Strömbeck also mentions that half the patients seen on follow-up study with

limbs that had been saved had numbness or paresthesias.

Some fragmentary data are available on 9 of our 14 patients who underwent embolectomy and survived. Of these, 6 have died, 3 of cerebral embolism, 1 of coronary closure, 1 of heart failure and 1 of carcinoma of the esophagus. Of the 3 patients living, 1 had a cerebral embolism with hemiplegia and the further course is unknown. Two others were living and well three and seven years, respectively, after operation.

There is also some information on 10 of the 44 patients who survived nonsurgical treatment. Five remained or became hemiplegic. One of these was well for seven years before dying of cerebral embolism. Another patient died two days after discharge, and another three years after discharge of coronary occlusion. Three patients were living in fair health two years after discharge.

Discussion

The treatment of arterial embolism is always undertaken as an emergency. It is a nonelective procedure. Patients cannot be referred at leisure to faraway specialists for this treatment. Every community where human beings suffer from rheumatic fever or arteriosclerosis will observe a regular, though small, incidence of arterial embolism. Any doctor, whatever his specialty, might be the nearest to a patient so stricken and be called upon to provide at least first aid. Immediate hospitalization and initiation of definitive treatment should be urged. This treatment does not have a fair chance unless the time factor is considered as paramount. Nystrom[7] has pointed out the benefits to be derived if the whole medical community participates in the treatment of these patients. From our study we have formed the opinion that operation should be performed in all cases in which local anesthesia can be used, with the sole exception of popliteal emboli. Also, aortic embolectomy, which requires a general anesthetic, is the treatment of choice for embolism of the aorta. Conservative treatment, although its results are good in some cases, is justifiable only when the embolism obviously does not endanger the limb, in the rare aortic embolism in which the patient cannot be brought into the proper condition to withstand a general anesthetic, and in popliteal embolism. It is emphasized that if one is forced to use conservative therapy alone it is essential that it be initiated with as much dispatch and urgency as is advocated for surgical treatment. Even though the embolism is for many patients the last milestone on the downward road of serious cardiac disease, lives are saved by embolectomy. It is difficult to doubt the value of the procedure when one reads case reports such as that contributed by Ravdin and Wood[44] in which a young man was reclaimed by aortic embolectomy for a very useful existence. Danzis[9] has said: "While the operative results are far from ideal, much suffering may be spared and many limbs and even lives be saved by prompt intervention and careful surgical technique."

Summary

A review of 179 arterial emboli in 98 patients is presented. One hundred and ten involved the limbs.

The salvage of 85.7 per cent of 21 limbs, which could be analyzed after embolectomy, is reported.

In 65.8 per cent of conservatively treated arterial emboli, the limb was preserved.

It is concluded that although available conservative weapons are valuable adjuncts to surgery, surgical embolectomy is the treatment of choice in peripheral-artery embolism.

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IDIOPATHIC HYPERLIPEMIA*

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IDIOPATHIC hyperlipemia, an apparently benign disorder of neutral fat metabolism of unknown etiology, has been reported six times since Buerger and Grütz[1] first described the syndrome in 1932. Thannhauser[2] reviewed the reported cases to the time of the publication of his monograph in 1940. The essential features of this disorder consist of a grossly milky blood serum due to increase in neutral fat content, together with enlargement of the liver and spleen. Xanthomatous lesions of the skin may also be present. Unexplained abdominal colic has occurred in half the cases. A moderate reduction in blood fats has followed dietary treatment, but normal values have not resulted.

Case Report

H. L., a 26-year-old married veteran, was admitted to the hospital on December 11, 1946, because of a chronic, nonproductive cough of 10 years' duration. This had become severer after an attack of bronchitis in the preceding July. He had had no other symptoms of any sort.

In early childhood skin lesions, which had exuded a yellow material, had developed on the legs, and later, between the ages of 9 and 10, flat, yellow plaques had appeared on the extremities. In 1944, while in Italy, the patient had experienced several brief episodes of cramp-like pain in the middle and upper abdomen, accompanied by nausea and vomiting. During hospitalization for these attacks lipemia and splenomegaly were first discovered. After prolonged study he was discharged from the Army. Since then he had remained free of gastrointestinal complaints.

His mother and three siblings were living and well. His father had died of "cancer of the bowel." There was no family history of diabetes mellitus or other metabolic disease.

Physical examination disclosed a well nourished man who was 5 feet 2.5 inches tall and who weighed 125 pounds. The skin and mucous membranes were normal, and there were no xanthomatous lesions. Examination of the heart revealed a soft, systolic murmur in the pulmonic area, which disappeared on deep inspiration. The lungs were clear and resonant, the abdomen was soft, and no tenderness was elicited. A firm liver edge was palpable 2 cm. below the right costal margin in the midclavicular line. The edge of the spleen was easily palpated 6 cm. below the left costal margin. Rectal examination showed external hemorrhoidal tabs. The remainder of the examination was within normal limits.

The temperature, pulse and respirations were normal. The blood pressure was 120/80.

Examination of the blood disclosed a red-cell count of 4,900,000, with a hemoglobin of 14 gm. per 100 cc., and a white-cell count of 4300, with 57 per cent segmented neutrophils, 4 per cent band forms, 36 per cent lymphocytes and 3 per cent monocytes. The urine had a specific gravity of 1.025 and gave a + to ++ test for albumin and a + reduction of Benedict's solution. The reaction was acid. No Bence–Jones protein was present. Microscopical examination of the sediment was negative. The serum cholesterol was 295 mg. and subsequently 205 mg. per 100 cc. after the patient had been on a fat-free diet for 48 hours. The serum bilirubin was less than 0.1 mg. per 100 cc. The alkaline phosphatase was 3.5 Bodansky units. The cephalin-flocculation test was + after 48 hours, the fasting blood sugar was 106 mg. per 100 cc., and the prothrombin time 88 per cent of normal; the total protein was 7 gm. per 100 cc., with 3.9 gm. of albumin and 3.1 gm. of globulin. Hemolysis of the erythrocytes began at 0.46 per cent sodium chloride and was complete at 0.38 per cent. The coagulation time was 6 minutes, and the bleeding time was 1 minute. A stool was negative for occult blood. The vital capacity was 3800 cc.

X-ray films of the skull, chest, spine, long bones and sinuses were normal. An intravenous pyelogram showed the left kidney to be rotated on its longitudinal axis and displaced slightly toward the midline by the enlarged spleen; the contrast substance was excreted to a normal degree, and no abnormalities were noted in the urinary tract.

On symptomatic treatment the cough, presumed to be due to chronic bronchitis, disappeared, and the patient was discharged on January 2, 1947, without dietary or other restrictions. On February 17 he returned for a blood lipid determination (Table 1), and immediately thereafter he began to suffer from malaise, anorexia, backache, headache, chills and fever.

Physical examination revealed herpes simplex on the lip; otherwise, the findings were unchanged from the previous admission.

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The temperature was 100.2°F., the pulse 96, and the respirations 16.

Examination of the blood showed a red-cell count of 4,100,000, with a hemoglobin of 13.4 gm. per 100 cc., and a white-cell count of 2410, with 32 per cent segmented neutrophils, 18 per cent band forms, 38 per cent lymphocytes and 12 per cent monocytes. The urine gave a ++ test for albumin and contained no sugar. The sediment was normal. Blood smears were negative for malaria. Blood cultures were sterile. No cold agglutinins were present in the blood serum. An x-ray film of the chest showed no change.

Four days after entry the patient became icteric, and the liver edge extended 10 cm. below the right costal margin. The stools became light colored, and the urine became dark, with a positive test for bile. The urinary urobilinogen was 1.8 Ehrlich units in 2 hours, the serum bilirubin 7.8 mg. per 100 cc. total, with a positive direct van den Bergh reaction, and the cephalin flocculation ++++. The white-cell count fell to 2000, with 36 per cent segmented neutrophils and 64 per cent lymphocytes.

The patient was placed on a high-carbohydrate, high-protein, low-fat (30 gm.) diet. His appetite rapidly returned, and after 6 weeks of bed rest, the serum van den Bergh, cephalin flocculation and urine urobilinogen had returned to normal. Repeated urinary specimens were bile free, but showed a + to ++ test for albumin and a + to ++ reduction of Benedict's reagent. Glucose (100 gm.) was administered by mouth. The fasting blood sugar was 85 mg. per 100 cc., and at ½ hour, 1 hour, 2 hours and 3 hours, respectively, 162, 128, 86 and 68 mg. per 100 cc. The urine gave −, + (olive) +++ (orange) ++ (yellow) and − reductions of Benedict's solution in the fasting, ½-hour, 1-hour, 2-hour and 3-hour specimens, respectively. The serum amylase was 11 units per 100 cc.

The patient was discharged on April 4, with instructions to continue the rigid low-fat diet. After a total of 9 weeks on this regimen, the serum lipids showed a marked decrease (Table 1).

On July 7 he reported that he felt perfectly well, but had not been following his diet rigidly. The serum lipids had returned to the original level (Table 1).

Two siblings of the patient were examined; the blood serum of neither was lipemic.

Table 1. *Blood Lipids in a Case of Idiopathic Hyperlipemia.**

Date	Total Fatty Acids	Neutral Fat	Total Phospholipids	Saponifiable Phospholipids	Total Cholesterol	Cholesterol Esters
1947	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
February 17† ...	3370	3202	328	290	250	100
April 30‡	1840	1612	207	—	204	118
July 7†	3730	3420	273	—	290	165

*Analyses performed by Dr. Siegfried J. Thannhauser.
†Normal diet.
‡Low-fat diet.

Discussion

Skin lesions have been observed in 4 of the 6 previously reported cases of idiopathic hyperlipemia. Three patients had yellowish, discrete papules, chiefly on the extensor surfaces of the extremities and on the buttocks. These lesions are also found on the lips, face, palate, eyelids, ears, fingers, toes and scrotum. One patient had a somewhat different type of lesion beginning as vesicles, which soon ruptured, leaving shallow ulcers that persisted for a number of months.[3, 4] The history of the patient reported above suggests that he had had both types of lesions in childhood, although the skin was free of xanthomatous lesions during observation.

Colicky abdominal pain has been reported in 3 cases. Exploratory laparotomy in 1 case[3, 4] and autopsy in a patient who died of an intercurrent disease[5] revealed no cause for abdominal pain. The history in the case presented above indicates that the patient had had such a pain in Italy in 1944.

Hepatic and splenic enlargement, varying in degree, has been uniformly observed in all the reported cases of idiopathic hyperlipemia. In Holt's patient the organs enlarged after each attack of abdominal pain at the same time that the blood lipids decreased. In 3 cases a decrease in hepatosplenomegaly occurred with the restriction of fat in the diet.

Whether patients with idiopathic hyperlipemia subsequently develop xanthomatous biliary cirrhosis is not known. None of the reported cases of idiopathic hyperlipemia have exhibited jaundice. The jaundice in the case reported above is believed to have been a simple infectious hepatitis. In xanthomatous biliary cirrhosis neutral fat is not elevated to the degree reported in idiopathic hyperlipemia, and there is a disproportionate rise in the total cholesterol.

Chronic pancreatitis may be associated with hyperlipemia as well as diabetes mellitus. In many cases the attacks of abdominal pain associated with pancreatitis do not appear differentiable from the pain noted in idiopathic hyperlipemia. It is possible that chronic pancreatic disease is related etiologically to idiopathic hyperlipemia. However, in the only autopsied case of this disorder a normal pancreas was observed.[5]

The prognosis in this condition appears to be excellent. Treatment with lecithin, choline, thyroxin, insulin, liver extract, anterior pituitary extract and lipocaic has not significantly altered the blood fats.[4] A low-fat intake has led to reduced blood fat levels, a subsidence of skin lesions and a decrease in the size of the spleen and liver.

Summary

A case of idiopathic hyperlipemia with hepatosplenomegaly is reported. The findings in the 6 cases of this disorder previously described are reviewed.

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STREPTOMYCIN TREATMENT IN ACUTE BRUCELLOSIS*

Report of a Case with Review of the Literature

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ALL three strains of Brucella are known to be sensitive to small concentrations of streptomycin in vitro.[1] This antibiotic has also been shown to protect chick embryos against infection with *Brucella abortus*[2] and to modify the infection to a considerable degree in guinea pigs.[3] Recent studies, however, throw doubt on the efficacy of streptomycin in experimental brucellosis in guinea pigs.[4] The reports that have appeared on the use of streptomycin in the treatment of brucellosis in human beings have so far been equally inconclusive.

Table 1 lists the significant data on streptomycin treatment in the cases reported in the literature. Reports in which neither blood levels nor daily dosage of streptomycin are clearly specified are not included.

Table 1. *Significant Data in Cases of Brucella Treated with Streptomycin.*

Author	No. of Cases	Total Dosage	Duration of Treatment	Daily Dosage	Blood Level	Result
		gm.	*days*	*gm.*	*microgm./cc.*	
Keefer[5]	25	—	5–16	3.0–4.0	—	Decrease in fever
	5	—	—	3.0	—	Decrease in fever
	10	—	—	2.0	—	No response
	5	—	—	3.0–4.0	—	No response
Nichols and Herrell[6, 7]	8	—	—	—	—	No response
	1	14.6	14	1.0	—	Doubtful
	1	43.0	36	1.0–2.0	—	Ultimate recovery after three courses of treatment, followed by splenectomy
	1	7.0	7	1.0	—	Doubtful
Reimann et al.[8]	1	54.0	7	1.0	1–4	Relapse after treatment; ultimate recovery.
		—	6	3.0	9–13	—
		—	1	4.0		—
		—	5	5.0	27	—
	1	24.0	7	4.0	12–19	Decrease in fever; no relapse.
	1	24.0	8	3.0	12	No response
Morgan and Hunt[9]	1	38.75	5	2.0	—	Temporary arrest of bacteremia; relapse after treatment.
		—	2	4.5	—	
		—	3	6.0	—	—
Pulaski and Amspacher[10]	6	8.0–63.0	10–20	1.0–3.0	—	No response
	1	32.0	20	1.2–1.8	16	Sulfadiazine given concomitantly; recovery.
	1	141.0	47	3.0	16	—
Howe et al.[11]	1	16.0	10	—	6–25	No response; relapse.
	1	23.0	6	—	16–47	No response
	1	20.5	6	—	3–28	No response; relapse.
Hall et al.[12, 13]	1	19.0	9	2.2	—	No response
	1	27.0	9	3.0	—	Doubtful
	1	118.0	31	3.0–5.0	—	No response; drug-resistant strain; eventual recovery.
	1	23.5	8	3.0	33–50	Improvement
	1	28.0	7	4.0	40–90	Improvement

Of the 45 cases of brucellosis reported by Keefer,[5] 30 showed decrease in fever, and 15 showed no response to streptomycin treatment. The incidence of relapse in these cases is not given. Nichols and Herrell[6, 7] have reported 11 cases of brucellosis, giving details in only 3. Only 1 of the patients with bacteremia gave evidence of improvement, after three separate courses of streptomycin, the last course following splenectomy. Reimann, Price and Elias[8] give data on 3 cases of brucellosis. Fever in the first 2 cases appeared to respond temporarily to streptomycin administration; the third case showed no response. In these cases, no blood cultures were taken during or after treatment and the length of the follow-up period is not specified.

Morgan and Hunt[9] present 1 case in which there was no clear-cut clinical response, despite temporary elimination of organisms from the blood stream. Pulaski and Amspacher,[10] in treating 8 patients with bacteremia due to Brucella, noted benefit in only 2 cases in which sulfadiazine was given concomitantly, and recommend this combined type of therapy in the treatment of brucellosis. Howe et al.[11] used streptomycin in 3 cases of acute brucellosis without appreciable change in any; 2 cases had relapses after treatment. Hall, Braude and Spink,[12, 13] in 2 cases of chronic brucellosis with bacteremia, claimed no clear-cut effect from streptomycin. In a third case, with endocarditis, these authors noted that organisms recovered during and after thirty-one days' treatment with streptomycin had developed marked resistance to the drug in vitro.

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In 2 additional cases, in which high blood levels were attained, these authors report improvement as a result of therapy. In 2 cases reported as brucellosis by Goelz[14] and Brier,[15] the diagnosis was inconclusive. A definite impression of the effect of streptomycin in the 6 cases of acute brucellosis reported by Finch[16] cannot be gained from the data presented, although a favorable response to treatment is said to have been obtained.

Because of the equivocal results observed to date, it seems worth while to present 1 more case of infection due to *Br. abortus*, in which streptomycin was used with some evidence of therapeutic effect.

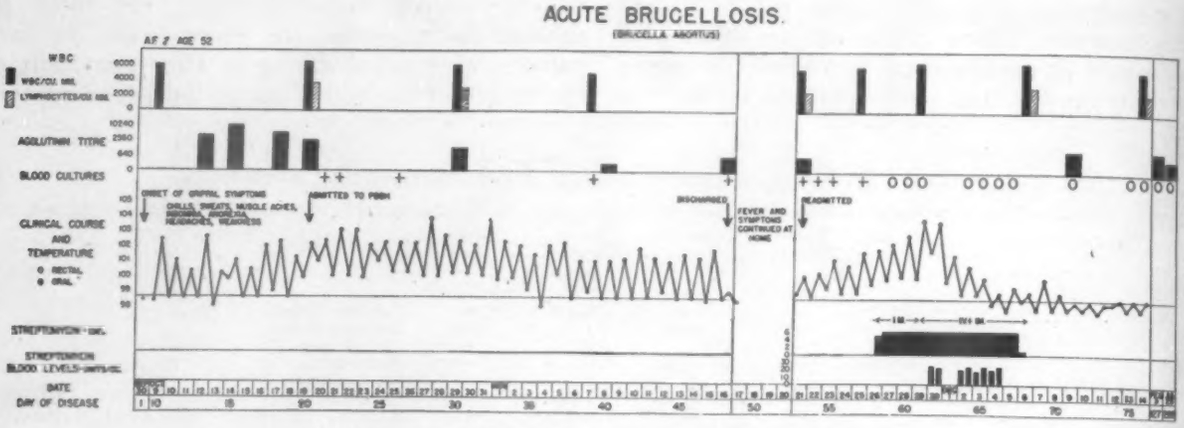

FIGURE 1. *Data in Case of Acute Brucellosis.*

Ten months after the onset of the illness and eight months after completion of treatment, blood cultures were negative, and the agglutination titer was 1:640. The patient remained well up to fifteen months after treatment.

CASE REPORT

A 52-year-old man, whose past medical history was not remarkable, was admitted to the hospital on October 19, 1946, 3 weeks after the onset of extreme malaise, anorexia, slight nasal congestion and dry cough. Two weeks before admission, he had had a shaking chill, which was followed by daily afternoon temperature elevations to 100 to 102°F. and profuse night sweats. He had consumed unpasteurized milk on numerous occasions prior to the onset of the illness. A blood specimen sent to the Massachusetts Department of Public Health 1 week before admission had shown a titer of agglutinins for *Br. suis* of 1:400, rising 4 days before admission to 1:5000. A presumptive diagnosis of brucellosis had therefore been made by the family physician.*

Physical examination showed a patient who appeared to be exhausted and was perspiring profusely. The mucous membranes were pale. The liver was palpable three finger-breadths below the right costal margin. The spleen was not felt at any time during the period of the patient's hospitalization. Physical examination was otherwise negative.

The temperature was 101°F. by rectum, the pulse 88, and the respirations 20. The blood pressure was 100/70.

Examination of the blood revealed a hemoglobin of 15 gm. per 100 cc. and a hematocrit of 45, falling to 39 during the ensuing month. The blood Hinton test was negative. The sedimentation rate varied between 1.4 and 1.6 mm. per minute (Wintrobe method) as determined on five occasions. The white-cell count was consistently found to be between 5000 and 6000, with 40 to 50 per cent lymphocytes. The urine on admission, as well as on four occasions during chemotherapy, showed no abnormalities. Blood cultures were taken into liver infusion and tryptic digest broth, and were incubated at 37°C. in candle jars (approximately 10 per cent carbon dioxide), none being discarded as negative before the end of 3 weeks. Thioglycollate was added to the cultures taken during the period in which the patient was receiving streptomycin. The increased carbon dioxide tension may also have served to reduce the action in vitro of what little streptomycin was added to the cultures with the patient's blood.[1] *Br. abortus* was recovered from the blood on numerous occasions prior to streptomycin therapy, and the strain was identified by growth on differential dye mediums and estimate of hydrogen sulfide production. During and after treatment, all blood cultures remained sterile. The strain was found to be sensitive, in vitro, to 2.0 microgm. of streptomycin per cubic centimeter of tryptic digest broth. The variations in the titer of agglutinins for *Br. abortus* are shown in Figure 1.

The course of the fever was typical of active brucellosis. Streptomycin did not become available for use in this case until 5 weeks after admission, and a control period of observation in which no chemotherapeutic or antipyretic agents were administered was thus allowed. Fifty-eight days after the onset of the illness, a course of streptomycin was started.† The patient was given a total of 60 gm., in daily doses of 6 gm. (1 gm. every 4 hours), over a period of 10 days. He complained of increasingly acute burning, aching and tender swelling at the sites of intramuscular injections, despite the presence of procaine in the injected solutions of streptomycin. By the 4th day of treatment, because of excruciating pain in both gluteal and quadriceps muscle groups, the patient was hardly able to walk, was acutely uncomfortable in any position in bed and was unable to sleep despite sedation. The mode of administration of the drug was therefore altered, so that he received 1 gm. intravenously every 4 hours during the day, each dose being dissolved in 400 cc. of physiologic saline solution and given over approximately ½ hour; only the midnight and 4-a.m. doses were given intramuscularly as before. This change had no appreciable effect on the established blood levels of streptomycin. Determinations were made shortly before and 1 hour after scheduled intramuscular intravenous doses, to ascertain the minimum and maximum blood concentrations obtained by each route. The blood levels varied between 20 and 25 microgm. per cubic centimeter of blood.

During the last 5 days of treatment, the temperature declined rapidly. The patient felt much improved, he suffered no more night sweats, his appetite increased, and the muscle soreness subsided promptly. Audiograms and vestibular-function tests were normal at the conclusion of

*We are indebted to Dr. F. F. Blumenthal, of Bridgewater, Massachusetts, for referring the patient to this hospital, and for his continued interest and co-operation.

†Streptomycin hydrochloride kindly supplied by Merck and Company, Rahway, New Jersey.

treatment, except for slight high-tone deafness. During the first few weeks of convalescence, he complained of definite unsteadiness of gait, occasional dizziness and questionable tinnitus, all of which may have been due to streptomycin toxicity. For approximately 8 months after the completion of therapy the patient continued to improve generally; he returned to work, and had no sign of recurrence of the infection. The vestibular symptoms diminished, but persisted in a minimal degree. On July 27, 1947, 10 months after the onset of illness and 8 months after the beginning of treatment, blood cultures were sterile, and the agglutinin titer was 1:640. Fifteen months after treatment the patient was still free of symptoms.

Discussion

In untreated cases of acute brucellosis, the degree to which recovery takes place is directly related to the efficiency of the individual immune mechanism. In the case presented above, the effect of streptomycin treatment was added to that of the immune response. Both these factors should therefore be considered in any attempt to explain the recovery.

Such an attempt is complicated by the nature of the disease, since, in the light of recent studies by Ruiz-Castañeda[17] confirming earlier observations of Smith,[18] Goodpasture and Anderson[19] and Buddingh and Womack,[20] brucellosis appears to be predominantly an intracellular infection. Meyer[21] has stated more specifically that "selective intracellular parasitism in mesenchyme cells of various organs is of greatest significance in the pathogenesis of Brucella infections." The titer of specific agglutinins by present methods of determination is probably the result of several constantly changing forces: the degree of host parasitization, or the total amount of antigen present, which is affected to a varying extent by the bactericidal power of the blood; the rate of production and total quantity of antibody; and the degree to which antigen and antibody react with each other within the host. A rapidly mounting increment of organisms, multiplying intracellularly and outstripping the production of antibody with which to neutralize circulating antigen, might be evidenced by a declining concentration of agglutinins. Conversely, with the curtailment of bacteremia, either spontaneously or by chemotherapy as in the case reported above, there is presumably some limitation of further host parasitization, and the agglutinin titer might be expected to rise if the immune response continues. A definite fall in agglutinin titer was observed during the first seven weeks of the patient's illness, and shortly after his abrupt clinical recovery, the titer started to rise again. It is possible that chemotherapy at the end of the eighth week of continued bacteremia spared this patient a more protracted course and allowed his own immune mechanism to become effective. However, the fact that resistance to and recovery from infection is not wholly dependent upon the presence of tangible antibody — that is, agglutinins — and must involve other less readily detectable immune factors is attested by the coexistence in the blood of organisms and circulating antibody, not only in brucellosis but also in other infectious diseases, such as typhoid fever and subacute bacterial endocarditis.

That streptomycin penetrates beyond the cell membrane is suggested by reports on the concentration of the drug in various tissues after its parenteral administration in man[22] and animals.[23] It is thus not illogical to suppose that in the presence of sufficiently high blood concentrations, maintained for adequate periods, streptomycin exerts bacteriostatic or bactericidal action on intracellular organisms. It may be significant that among previously reported cases of brucellosis in which it was possible to decide whether streptomycin treatment had been effective, temporary or lasting benefit was demonstrated only in patients in whom the blood levels reached or exceeded 20 to 30 microgm. per cubic centimeter or in whom the daily dose at any time approached 6 gm. It is of interest in this connection that the patient described above received 6 gm. a day for ten days, maintaining blood levels between 20 and 25 microgm. per cubic centimeter and recovered completely, albeit with minimal signs of streptomycin toxicity. It is probable, however, that the effect of antibiotics on intracellular infections is not all a simple matter of dosage and blood levels, since tularemia, also primarily an intracellular infection, is far more susceptible of cure with streptomycin than brucellosis appears to be.

Summary

An acute case of brucellosis, in which streptomycin was given in large doses, with apparent success, is presented in detail. In a review of all previously reported cases of brucellosis treated with this antibiotic, it appears that patients in whom the highest blood levels of drug were maintained for even relatively short periods showed more signs of response than those in whom lower blood levels were maintained over relatively longer periods. Therapy at high dosage, however, is not without risk of streptomycin intoxication, as evidenced by the slight though definite vestibular impairment persisting in the case reported.

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THE VALUE OF A SPECIAL AURICULAR LEAD AND OF CAROTID-SINUS PRESSURE IN THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF TACHYCARDIAS AND OTHER DISORDERS OF THE HEART BEAT*

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BOSTON

ONE of the chief uses of the electrocardiogram in clinical medicine is in the differential diagnosis of cardiac arrhythmias. Ordinarily, a definite diagnosis of the disorder of the beat can be made easily from the standard leads, but in patients with tachycardias it may be difficult or impossible to be certain of the type of arrhythmia present because the auricular waves may be small or hidden in the QRS or T complexes. The same statement is occasionally true with slower rates. Hence, a lead in which the electrodes are so applied as to show maximal potential changes developed by auricular activity may be of help under such circumstances.

Lewis[1] first noticed in 1910 that the F waves of auricular fibrillation were best brought out in electrocardiograms in which the exploring electrodes were placed over the region of the right auricle. Later, Ackermann[2] demonstrated that the auricular waves were well defined when needle electrodes were placed in the second and fifth interspaces to the right of the sternum. Subsequently, many studies have been made, many of which have dealt with distinguishing the activity of the two auricles, a problem with which we are not here concerned. Luisada[3] has summarized knowledge of auricular leads and of auricular disorders. Among these studies an important advance was made in 1934 by Lieberson and Lieberson,[4] who introduced the technic of the esophageal lead. This has been utilized frequently since then for auricular disorders but especially in the diagnosis of posterior myocardial infarction. Recently, Butterworth and Poindexter[5] have emphasized the value of the esophageal lead in clinical electrocardiography in the diagnosis of tachycardias and arrhythmias.

In January, 1937, the employment of a special auricular lead was first introduced at the Boston City Hospital by one of us (J. M. F.). In the succeeding ten years this lead has been routinely employed, often in combination with carotid-sinus pressure, when the type of rhythm was not clear. During this period the procedure has been carried out about 2600 times, which represents 4.3 per cent of the total of 60,000 records taken. Our procedure has consisted in taking electrocardiograms by the usual technic including routine precordial leads. In addition, we have obtained the special auricular lead by removing the electrode from the left arm and placing it on the chest in the third interspace just to the right of the sternum. Tracings are then taken with the control switch successively at Leads I and 3. This has given records that are CR and inverted CF (labeled in the illustrations as CF'_A). It has been found that the auricular waves are seen best sometimes in one and sometimes in the other lead. Since we have not been concerned in this lead with the details of contour of the P waves or other complexes, the inverted CF lead has been no disadvantage and technically has been a more rapid and simple procedure than a CF lead taken in the conventional way.

In addition, while these leads are being taken pressure has been applied alternately to the right and left carotid sinuses or to both at once. Although it is well known that such vagal stimulation may abolish certain paroxysmal tachycardias or produce a temporary increase in auriculoventricular block in auricular flutter and tachycardia, thus making it easier to make an electrocardiographic diagnosis, it seems to be less widely appreciated that this maneuver may cause a very slight transitory slowing in

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patients with normal heart rates, both with sinus rhythm and with arrhythmias. In such cases, in which the P wave may have been hidden in the preceding T wave or in its own QRS or T complexes, the transitory slowing thus produced may uncover the hidden P wave.

The procedure has been employed in all obscure cases, especially in those with tachycardias of any type. In particular it has been of value in auricular flutter with 2:1 block. It has also been of great help in the diagnosis of paroxysmal ventricular tachycardia, in which the demonstration of an independent auricular rhythm in this lead has been strong evidence in its differentiation from other conditions giving similar electrocardiographic patterns. The auricular waves of auriculoventricular nodal rhythms have also been frequently clearly brought out, and the method has been useful in the differentiation of such rhythms from auricular fibrillation with complete heart block.

Figures 1 to 6 illustrate the value of the lead in some of these disorders of the beat.

The technic is simple, can be carried out quickly and produces no discomfort for the patient. It is thus suitable for routine employment in clinical electrocardiography. Through its use correct diag-

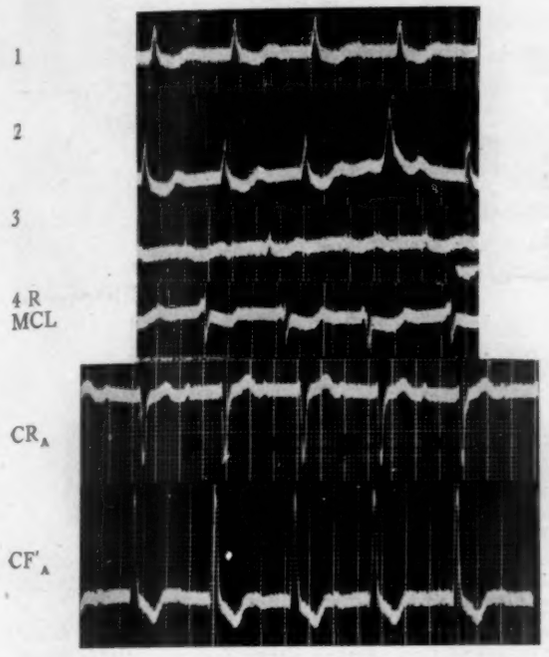

FIGURE 1. *Normal Sinus Rhythm, with Prolonged Auriculoventricular Conduction Time.*

The P waves are not definite in the usual leads but appear clearly in CR_A, as well as in CF'_A.

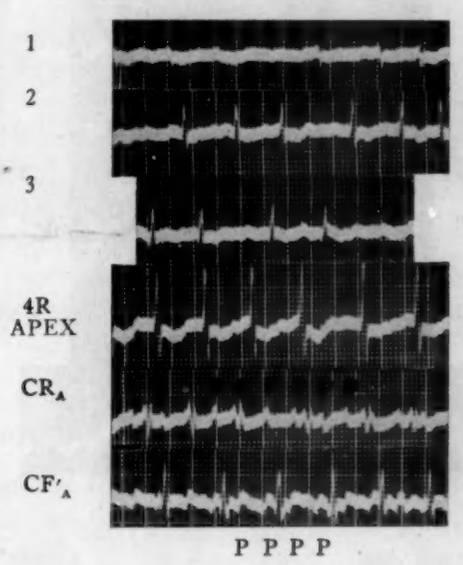

FIGURE 3. *Auricular Flutter, with Varying Auriculoventricular Heart Block.*

The P waves are made out with difficulty in the usual leads, but are clearly shown in both CR_A and CF'_A.

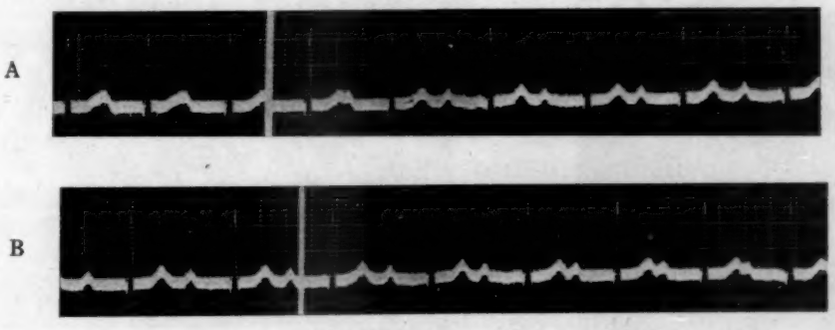

FIGURE 2. *Continuous Record of Lead 2 Only.*

Incomplete auriculoventricular block with P waves superimposed on preceding T waves. A shows an electrocardiographic tracing when carotid-sinus pressure is applied, and B a tracing when pressure is released. Carotid-sinus pressure produces moderate slowing, thus separating the T and P waves and enabling a diagnosis to be made.

noses have been made early, and proper treatment instituted promptly. Other special leads that have been used for this purpose, in particular the esophageal lead, involve a much more formidable procedure. Although the esophageal lead is probably the best for the elucidation of auricular activity in clinical electrocardiography, we have found that the third-right-interspace lead has made it unnecessary to resort to the esophageal lead except in very rare cases.

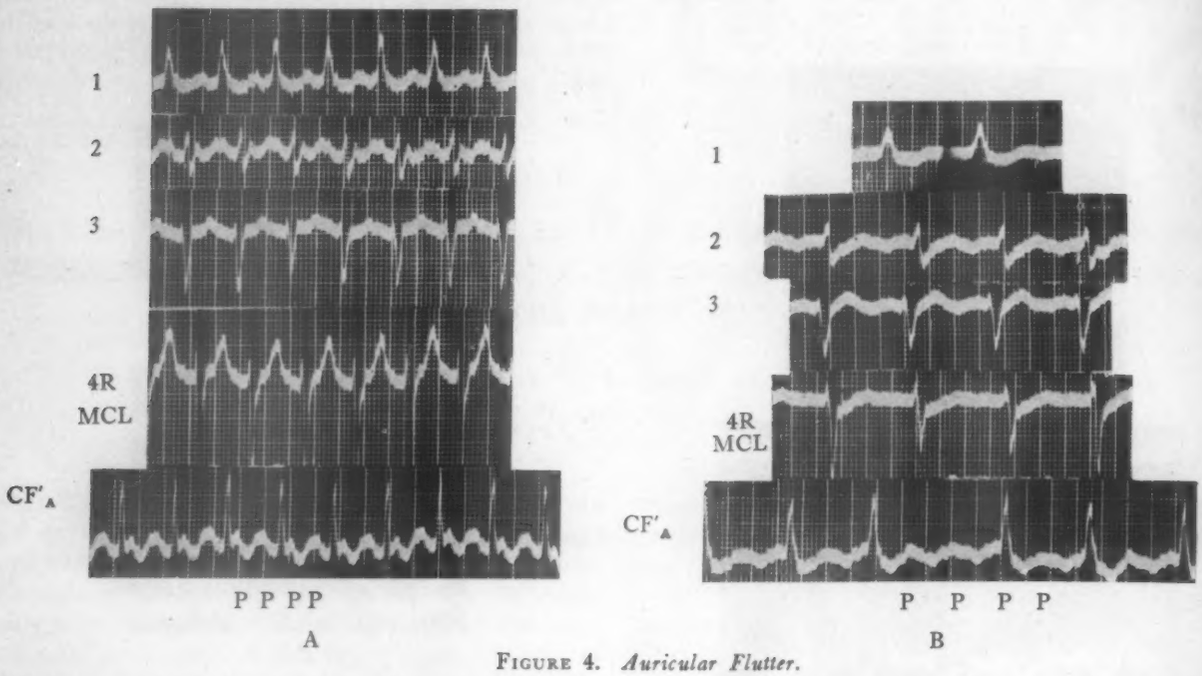

FIGURE 4. *Auricular Flutter.*

The first record (A) *shows 2:1 heart block with P waves at a rate of 286, much more easily made out in CF'A than in the standard leads. The second record* (B), *after quinidine, shows the persistence of flutter with a slower auricular circus movement (172) that can be conclusively diagnosed only in CF'A.*

The standard texts on electrocardiography occasionally mention special leads for bringing out the P waves. The discussion, however, is usually confined to a single arrhythmia such as auricular flutter

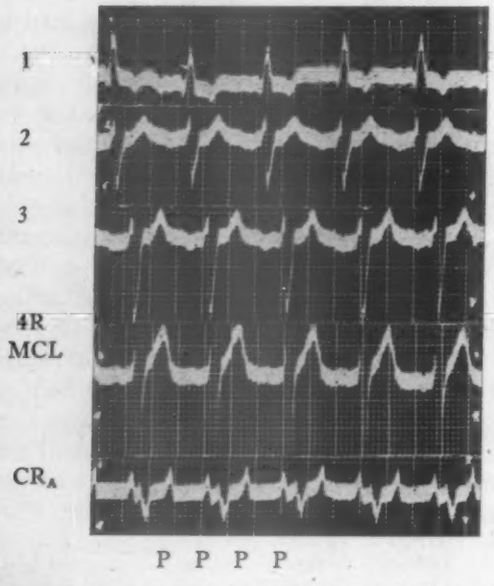

FIGURE 5. *Paroxysmal Auricular Tachycardia with 2:1 Heart Block.*

Auricular rate, 214; ventricular rate, 107. Diagnosis can be made only in CRA.

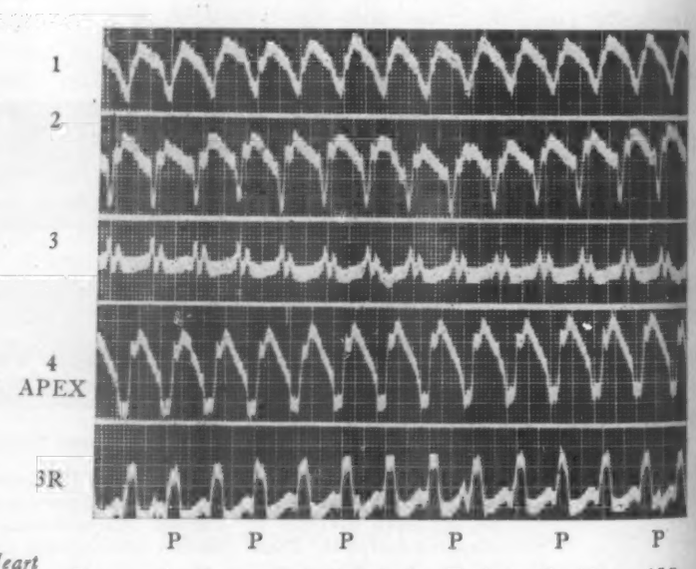

FIGURE 6. *Paroxysmal Ventricular Tachycardia (Rate, 154).*

The independent auricular rhythm at a slower rate (64) can be made out only in the auricular lead, CRA (labeled 3R).

and is easily overlooked, and the wide usefulness of the lead is not emphasized. It is certainly clear that the majority of physicians who are doing electrocardiography are unaware of the value of this procedure. Whether the conventional CR_1 or CF_1 would reveal as much information concerning auricular activity as the auricular lead is not evident from this study, since such leads have not been taken continually in this laboratory.

Summary

A special electrocardiographic lead that has proved of value in the identification of auricular activity is described. This consists of the placement of the left arm electrode over the third interspace to the right of the sternum and taking the electrocardiographic tracings successively in Leads 1 and 3. At the same time the application of carotid-sinus pressure is carried out. This procedure is useful in routine clinical electrocardiography in the diagnosis of tachycardias and of other arrhythmias when the P waves are not readily evident.

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MEDICAL PROGRESS

DIABETES (Continued)

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BOSTON

Metabolic Changes

Clinical reports as well as chemical studies emphasize certain new features in diabetic acidosis. The case report of Holler[13] showed that it is possible for a patient in diabetic acidosis to develop a critically low level of potassium in the blood serum, with paralysis of respiration that may be relieved by the administration of a potassium-containing solution.

Martin and Wertman[14] have analyzed serial measurements of the serum potassium, magnesium and calcium concentrations in 14 patients with diabetic acidosis (carbon dioxide combining power below 9 milliequiv. per liter). Three patients were comatose on admission, 3 were semicomatose, and 8 were conscious; 1 patient, admitted in coma, died. In addition to the electrolytes mentioned above, serum sodium, total protein, blood sugar, carbon-dioxide combining power and nonprotein nitrogen were determined on every patient; reaction, albumin-globulin fractionation and serum inorganic phosphorus determinations were made on a few patients.

In addition to the usual findings of acidosis, hyperglycemia and hemoconcentration, fluctuations in the serum potassium, magnesium and phosphorus concentrations were observed during the course of therapy. The serum potassium was above 6 milliequiv. per liter in the 5 patients on whom the determination was made on admission, the highest being 10.3 milliequiv. During therapy, the serum potassium was usually diminished within the first twenty-four hours and frequently fell to very low values (1.9 and 2.18 milliequiv. per liter). The potassium concentrations usually returned to normal levels within two or three days.

The serum magnesium, which was determined in 5 cases on admission, was slightly elevated in 2, normal in 2 and slightly below normal in 1. In most patients the serum magnesium fell at some time to abnormally low values, and then gradually rose. There was a rough correlation between the state of consciousness on admission and the serum magnesium concentrations.

Serum calcium concentrations were generally normal, although the total circulating calcium may have been reduced owing to the hemoconcentration.

The serum sodium concentration was either normal or somewhat low on admission, but soon after therapy was begun came into the normal range.

Inorganic phosphate determinations were made on only 2 patients, and in both the changes correlated with the serum potassium and blood sugar levels during therapy, which in all patients consisted in

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varying amounts in physiologic saline solution, one sixth molar sodium lactate, 5 per cent glucose, plasma and insulin.

Martin and Wertman[14] point out the similarity between the marked muscle weakness shown by several of the patients and that seen in familial periodic paralysis, another condition associated with low serum potassium concentration.

Holler et al.[15] have described patients who developed a similar syndrome during therapy for diabetic acidosis or coma. Therapy with potassium produced dramatic improvement.

In interpreting the changes in serum potassium concentration, Martin and Wertman[14] mention possible changes in urinary excretion or use of the potassium in carbohydrate metabolism. Since magnesium is, like potassium, nitrogen and phosphorus, an important intracellular component, it is not surprising to find that the movement of magnesium follows that of the other three compounds. However, as the authors point out, until intracellular concentrations of these substances are known it will be difficult to interpret adequately changes in serum concentration. Atchley et al.[16] showed that with the negative nitrogen balance that occurred in diabetic patients after the withdrawal of insulin, a negative phosphorus and potassium balance could be demonstrated as well. One might, by combining the data of Martin and Wertman with that of Atchley and his associates, assume that there is an intracellular depletion of potassium with increased serum concentration and loss in the urine during the period of insulin lack. On administration of insulin, the reverse would be true, but because of the potassium loss in the urine a body deficit exists, thus reducing the serum potassium concentration. If this interpretation is correct, the administration of potassium as therapy is called for, as the authors suggest.

The warning given by the authors against the administration of potassium to diabetic patients in shock is well taken, and, in fact, one might even say that potassium should be administered only very cautiously, or not at all, until adequate urinary output has been established. Several reports of dangerously high blood potassium concentrations have been published and have been added to and reviewed by Finch, Sawyer and Flynn.[17] It is especially noteworthy that a flaccid paralysis resembling that seen with low serum potassium may result from potassium intoxication.

Errebro-Knudsen[18] studied two healthy male medical students to determine the effect of intense muscular exercise on ketone-body formation. Both were trained sportsmen and trained for two months in riding on the bicycle ergometer so that they could perform work at about 1100 mkg. a minute for upward of three hours and forty minutes — this is really exhausting physical work.

For three days before the first experiment they lived on a mixed diet and then determinations were made. The second experiment was carried out after two days on a diet rich in fat and poor in carbohydrate. Thus, the total calories were between 3000 and 4000 for each diet. On the high-fat diet the figures were 57 gm. of carbohydrate, 30 gm. of protein and 398 gm. of fat. The students weighed 74 kilograms and 67 kilograms, respectively. On a mixed diet the total ketone bodies during work rose very slightly, from 0 in one experiment to 2.4 mg. per 100 cc. On one day the values started at 5.2 mg. and fell to 3.5 mg. at the end of the work period. Measurements were also made during the period following cessation of the exercise, and in each case a striking increase in ketone bodies occurred from three to twenty-three minutes after the end of the exercise. The values rose from 4.5 to 11.1 mg. per 100 cc. as an example. The respiratory quotient rose during the period of actual exercise from 0.78 to 0.84 and then fell back to 0.78, but declined perceptibly to 0.70 during the fifteen to twenty minutes following the cessation of exercise. In the next twenty minutes it rose to 0.74. It seemed evident, therefore, that with the cessation of muscular exercise the fuel utilized changed from carbohydrate to fat. However, it also shows that the low respiratory quotient was due to an oxidation of lactic acid accumulated during work. This could be explained by a retention of carbon dioxide.

The students who had been on a low-carbohydrate, high-fat diet started with respiratory quotients of 0.69 and 0.73. During work a rise in respiratory quotient to 0.73 in 1 and 0.77 in the other took place. The increase in blood acetone values was studied throughout the work period from 6 in one case and 12 in the other to 8 and 15 mg., respectively, with a further increase during the resting period up to 13 and 24 mg. per 100 cc., respectively. The blood sugar values showed only a slight decline in all the experiments from about 80 mg. to 54 mg. per 100 cc. in the experiments on a high-fat diet, with a much slighter decline in the experiments on a mixed diet.

One of the reasons for undertaking these experiments was to determine whether or not the fatigue experienced on a high-fat diet is really due to the accumulation of ketone bodies. The change in concentration of ketone bodies was so slight at the end of the work period as to lead to the conclusions that the fatigue is not due to ketone bodies.

Hyperglycemic Action of Highly Purified Alkaline Phosphatase

Professor William Kerppola, of Helsinki, Finland, was kind enough to provide the following abstract of his recent work, *On the Hyperglycemic Action of Highly Purified Alkaline Phosphatase*, which is now in press.

Highly purified alkaline phosphatase has been prepared from fresh cow udders. The strength of this preparation exceeds about five thousand times that of the first basic solution and contains about 35,000 active units (Alberts) in 1 cc. This amount may be capable of liberating about 20 gm. of glucose.

The preparation can be injected into animals and human beings without any local or general reaction. The blood picture remains unchanged.

When phosphatase is injected intravenously in rabbits during fasting the blood sugar increases suddenly and receives its highest value in an hour. Afterward it stays at an even height for about five hours and then decreases rather abruptly during the next two hours and comes gradually back to its initial value. No sugar was observed in the urine — not even when the blood sugar values were high. If phosphatase is injected subcutaneously in rabbits the blood sugar value remains unchanged but increases suddenly after seven to nine hours. The blood sugar value falls rather quickly and returns to the initial level in four to six hours. If a phosphatase is injected continuously once a day the blood sugar remains elevated as long as the treatment is continued.

If a glucose-tolerance test is made on rabbits during the phosphatase treatment, and if the curve obtained is compared with a corresponding one obtained without this treatment, a substantially raised and prolonged curve may be noted in most of the phosphatase-treated animals.

The decrease of the blood sugar value in rabbits produced by insulin injections is, under the influence of phosphatase, distinctly smaller than that in nontreated animals.

The glycogen values in the liver and the muscles of the treated animals do not differ from those of the nontreated animals.

The action of alkaline phosphatase on blood sugar seems to be quite the opposite of that of insulin.

Convulsive States in Diabetes

Convulsive states in diabetes are frequently encountered. The differential diagnosis is often difficult because in younger patients epilepsy is not uncommon. It was observed in 50 cases at the George F. Baker Clinic among children, and these were proved with abnormal electroencephalograms. The following opinion was expressed by Dr. Priscilla White[19]:

> Hyper and hypoglycemia have been suspected as causes. It is possible that hypoglycemia merely reveals the latent case. A few cases have had serious progression. More have apparently subsided with sedation therapy which has been followed with improvement in electroencephalographic tracings. Of some interest is Case 15322 whose similar twin does not have diabetes. The electroencephalograms reveal similar deviations from the normal. The diabetic has epileptiform attacks in the absence of hypoglycemia. The non-diabetic twin has had none.

In a preceding edition from the same clinic Dr. Howard F. Root[20] reported the autopsy findings in 2 cases:

> Case 7089 developed diabetes in March, 1920 at the age of two years and three months. Feeble-mindedness and epilepsy were evident at the age of eight years and she died in a convulsion at the age of twenty years. The histological diagnosis after examination of the brain was retarded development of the cortex, cerebellar degeneration (granular layer) and degeneration of the islands of Langerhans. For a detailed account of this patient see Case 2 in the paper of Ross and Dickerson. Case 11499 developed diabetes at the age of 4.3 years and epilepsy at 4.8 years. He died of bronchopneumonia caused by aspiration of food during a convulsion. In these 2 cases the marked mental deterioration during life and the extensive pathological changes found in the brain at autopsy suggested some congenital cause or at least damage to the brain produced by some other cause than hypoglycemia.

Ellenberg and Pollack[21] have discussed the problem with detailed reports of 2 cases and with the results of pathological examination in 1. Each patient had uncontrolled diabetes and showed repeated hospital admissions for ketosis or insulin reactions, and in the fatal case detailed study of the brain was made, resulting in the diagnosis of degenerative encephalopathy of unquestionably toxic origin:

> Sections of the frontal lobe, stained with hematoxylin-eosin, disclosed several arachnoid cell clusters in the leptomeninges. The nerve cells of the cortex presented a diversity of degenerative changes. Some were markedly swollen; many, however, were shrunken and contained pyknotic nuclei, while some contained finely granular, deeply staining oval nuclei with an occasional enlarged nucleolus. There were other cells in which it was difficult to distinguish nucleus from cytoplasm. The outline of some cells was irregular and occasionally the cytoplasm was poorly defined. Satellitosis was increased. With Nissl stains, marked central chromatolysis was seen in some areas. The Nissl substance itself was usually finely granular, diffusely scattered through the cytoplasm or concentrated at the periphery at the base of the cell. Some cells stained very faintly. Both cortex and subcortex showed marked and diffuse gliosis. The blood-vessels were engorged. Similar though less marked changes in the nerve cells were seen in the tegmentum, pons and medulla.

In the second case dilantin, phenobarbital and tridione were each tried in full therapeutic dosage, with no measurable beneficial effect on the frequency or severity of the attacks:

> An electroencephalogram made in April, 1947 again showed alpha waves with frequencies as low as 7.5 per cent with rare bursts of 6 per second activity and some single 3 per second waves. Hyperventilation did not increase the amount of slow activity. A record taken 10 minutes after the intravenous injection of 50 cc. of 50 per cent glucose showed the same characteristics.

In their discussion the authors suggest several possibilities: the convulsive seizures are the manifestations of irreversible cerebral changes following repeated attacks of insulin hypoglycemia; the changes are independent of the diabetes and are actually an influence in the causation of repeated shocks; the attacks are evidence of coincidental epilepsy. They cite the possibility suggested by Greenblatt, Murray and Root that the cerebral changes are independent of the diabetes and insulin hypoglycemia and actually instigate the frequent reactions, because abnormal electroencephalograms

were encountered in 51 per cent of the problem patients with diabetes. The frequency of actual epilepsy in patients with diabetes provides a most complicating factor, and all peculiar insulin reactions should be studied with this possibility in mind.

Electrocardiographic Changes

Changes in the electrocardiogram in diabetic acidosis have been described consisting of depression of the ST segment, lengthening of the QT interval and alternation in the T waves. The reversibility of these changes in a short period has suggested that changes in the electrolyte gallop were important factors in causing abnormalities. Martin and Wertman[22] studied 12 patients who entered the hospital in severe acidosis with the carbon dioxide combining power of the blood under 9 milliequiv. per liter. Chemical determinations in all cases included serum calcium, potassium, sodium and magnesium levels, total plasma protein, blood sugar and carbon dioxide combining power. Sagging of the ST segment was a prominent feature when acidosis was marked, but it usually disappeared within twenty-four hours. In 19 cases of such depression of the ST segment the reaction or the blood carbon dioxide was low in 16. There was no correlation in this series between these changes and the serum potassium level. Thirty-seven records showed prolonged QT intervals, many of these occurring one to four days after intensive therapy had been started. Sixteen of these were associated with low total or ionized serum calcium or potassium, but in 21 records, that is, 57 per cent of the patients whose records showed prolonged QT intervals at normal levels of serum calcium, a high degree of correlation between low T waves and low serum potassium levels was observed. In explanation of these changes the authors point to the various factors that may be present: the relation between extracellular and intracellular electrolytes, cardiac nutrition as affected by low insulin levels and the effects of anoxia and nitrogen retention. Actually the reaction values were as low as pH 7.28, 7.05 and 7.12 in 5 cases studied, but the remainder of the series did not have a determination of the reaction. Low levels of serum potassium included one of 1.9 and others as low as 2.18 and 3.2 milliequiv. per liter. In 11 cases with potassium levels under 4.2 milliequiv. per liter 9 showed low or isoelectric T waves. It is well known that with high potassium levels in the blood serum high T waves may occur. With higher levels of serum potassium, depression of the ST segment will occur, and actual intraventricular block occurs at the level of 10 milliequiv. and final cardiac arrest at 14 to 15 milliequiv. per liter.

The study emphasizes, however, the temporary character of these changes when adequate treatment for diabetic coma is given.

Arteriosclerosis

In 1928 Joslin[23] wrote as follows:

> The diabetic lives and dies in the arteriosclerotic zone. Lives in it because two-thirds of the 4592 true diabetics in the present series originated after 39 years of age; dies in it because although the average age at death of 339 cases in the Naunyn Period was 44.8 years, the average age at death of the 607 fatal cases in the present Banting Epoch is 54.2 years, and for the last year's 60 fatal cases was 59 years. During 1925 of all the diabetics who died in Massachusetts 86 per cent were above the age of 50 years. This is the year of age in which diabetes develops most frequently for men, the most common quinquennium for both sexes being between 49 and 55 years.

Today diabetic coma having dropped to 3.1 per cent as a cause of death, the duration of the disease having increased from 4.9 to 14.1 years, and the average age at death of the diabetic cases having risen to 64.5 years, it is not surprising that cardiovascular disease causes 66.6 per cent of diabetic fatalities. A generation ago diabetic patients did not live long enough to contract hardening of the arteries.

Despite the mounting incidence of arteriosclerosis in diabetes, our group is decidedly not pessimistic. Over a generation ago, when diabetic coma claimed 63.8 per cent of our cases, we acknowledge that we felt it represented the culmination of the disease and was the act of God, but we learned our mistake five years before insulin was discovered. Today we do not believe that arteriosclerosis represents the end of the diabetic patient either in consequence of the disease or as a coincident complication. We are firmly convinced that on the whole our patients who know the most, have followed treatment most assiduously and have received from our hands what we consider our best methods of treatment not only have done the best but also show the least number of arteriosclerotic lesions. We may not have more than 8 per cent of children, as studied by Dr. Priscilla White and later reported in this review, who are free of the disease after twenty years, but we do have a few cases of severe diabetes at the very onset in children who remain free from arteriosclerotic lesions after twenty-five years of diabetes. The recovery from impending coma by Nathaniel Potter, founder of the Sansum Clinic, in 1917 led the way to other recoveries from diabetic acidosis, and we are confident, as time goes on, that the medal, which the Diabetic Fund has created for patients with diabetes of twenty-five years' duration without evidence of degenerative disease in eyes, vessels and kidneys, will eventually be granted to many patients throughout the world. Today, the question is not so much the appalling incidence of arteriosclerosis in diabetes of long standing but what patients and doctors are going to do about it.

Substantiation of the studies of Root, Bland, Gordon and White[24] in their comparison of the

incidence of coronary disease and angina pectoris in nondiabetic and diabetic persons has been furnished by Stearns, Schlesinger and Rudy,[25] whose conclusions are as follows:

> Functionally significant coronary artery disease was disclosed in approximately three fourths of the hearts of 50 diabetic patients by means of postmortem injection plus dissection technic. One third of these patients had died of acute coronary heart disease. One quarter of the entire group had had angina pectoris. Among diabetic women over the age of 40 the incidence of significant coronary arteriosclerosis, of angina pectoris and of death due to coronary artery disease is as great as among diabetic men. This is in sharp distinction to the sex difference in these respects in the non-diabetic population. Angina pectoris, deaths due to acute coronary disease and congestive heart failure all are more common when hypertension is present in diabetic patients than when the blood pressure is normal. The severity of the coronary arteriosclerosis is correlated with the duration but not with the severity of the diabetes. Early detection of the symptoms of coronary artery disease in persons with diabetes is necessary if the sequelae of coronary arteriosclerosis are to be postponed or avoided. Mild hyperglycemia is preferable to a regimen which may result in insulin hypoglycemia and the attendant risk of precipitating myocardial infarction.

The relation of vascular disease to diabetes in childhood has been investigated by White.[26] Of 350 patients whose onset of diabetes occurred under fifteen years of age and who had survived twenty years or more of diabetes, 200 were examined in detail after they had had diabetes for twenty years or were known to have had arteriosclerotic lesions prior to the twentieth year of the disease. These patients are actually young adults. One hundred and ninety, or 95 per cent, are between the ages of twenty and thirty-nine years, and 10, or 5 per cent, were over forty. The sex distribution was even. Eight per cent of the patients were Jewish. The peak of age of onset was younger by seven years than it is in our entire juvenile series — namely, five years of age, compared with twelve years in all patients.

The total incidence of vascular disease was demonstrated in 184 cases or 92 per cent. The lesions were as follows: cerebrovascular disease, 2.5 per cent; coronary insufficiency, 8 per cent; hypertension, 40 per cent; nephritis, 50 per cent; calcified arteries, 75 per cent; retinal hemorrhages, 80 per cent; and retinal sclerosis, 85 per cent.

One must refer to the original article for details, but in the course of this review Dr. White made a very definite contribution to an estimate of the control of diabetes — as contrasted to lack of control — by establishing criteria. As indexes of control, coma, hyperglycemia, hypercholesterinemia and hepatomegaly were utilized. The results are shown in Table 7. Thus, the frequency of coma was only 17 per cent in the patients little affected with arteriosclerosis, 38 per cent in those moderately affected and in 70 per cent of those who were incapacitated. The following are the conclusions of the article:

> Whereas 8 per cent of 200 survivors were free from vascular lesions, 92 per cent had them.
>
> These statistics are the worst possible because they did not have modern diabetic therapy for 50 per cent of their diabetic lives. And, unfortunately, comparison of patients treated with modern methods cannot be made until 1950, for it requires 15 years of diabetes for vascular lesions to become manifest to the clinician. Protamine zinc insulin was introduced into this country in 1935.
>
> Poor control of diabetes paralleled the severity and frequency of the lesion.

TABLE 7.

TYPE OF PATIENT	NO. OF CASES	PATIENTS WITH COMA	HYPERGLYCEMIA*	HYPERCHOLESTEROLEMIA†	HEPATOMEGALY
		PERCENTAGE			PERCENTAGE
Normal, and retinal sclerosis only.....	28	17	28	25	0
Moderately affected by vascular disease ..	114	38	50	54	22
Incapacitated by vascular disease.....	50	74	54	47	36

*Blood sugar of 40 mg. per 100 cc.

†Blood cholesterol of 230 mg. per 100 cc.

Particularly notable in this study was the demonstration that pelvic arteriosclerosis was common and especially that it was of prognostic import for the fetus in pregnant patients with diabetes. Dr. Joseph H. Marks, roentgenologist at the New England Deaconess Hospital, permits me to state that in a study of 75 nondiabetic young women under forty years of age (a comparable age group to Dr. White's series), he found calcified pelvic arteries in only 1 case. And Dr. Marks also allows me to add that all but 1 of 19 cases of calcification of the vas deferens occurred in diabetic patients.

Dolger[27] studied 200 patients with diabetes of twenty-five years' duration, and among these there was not one who escaped vascular damage as shown by retinal hemorrhages and albuminuria or hypertension, or both, in varying degree:

> The group investigated consisted of 16 whose age of onset of diabetes was below 10 years; 39 whose age of onset was between 10 and 20 years; 22 between 20 and 30 years; 43 between 30 and 40 years; and 80 between 40 and 50 years. Retinal hemorrhage was the predominant lesion when diligent search was made routinely, and it often preceded the appearance of albuminuria and/or hypertension. All three lesions appeared in the patients regardless of the age of onset or degree of severity of the diabetes, the need for insulin, the type of diabetic "control" or diet employed, the blood cholesterol levels, or the absence of x-ray evidence of arterial calcification.
>
> Every diabetic would seem at present to be doomed to the inexorable development of vascular damage despite the benefit of insulin in prolonging life. At most, 25 years of freedom from arteriosclerosis can be offered even to the juvenile diabetic.

In a subsequent article Dolger[28] pointed out that "Careful scrutiny of the retina of each patient over the course of years indicated that the earliest clinical manifestation of vascular damage can be found in the eye." In the discussion that followed he reported that vitamins C and P, rutin and hesperidin did not influence retinal hemorrhages significantly because of spontaneous remissions and exacerbations displayed by these lesions, and he considered that work being done with cytochrome C or related oxidated enzymes was far more provocative and pertinent than vitamin research. The usefulness of determinations by capillary fragility proved, in his hands, so variable as to be valueless, being positive one day, negative in twenty-four hours and positive again a week later.

It is the impression of Dr. Priscilla White, who has followed the progress of our cases of retinitis proliferans, especially in young diabetic persons, that there has been much less rapid progress of these lesions since the introduction of rutin. Furthermore, she has not noted the wide variations of capillary fragility observed by Dr. Dolger. Dr. Howard F. Root, who especially has been concerned with the use of rutin in our entire clinic, substantiates her opinion.

TABLE 8. *Control of Diabetes with Separate Injections and with Mixtures.*

Type of Diabetes	Results	Separate Injection	Syringe Mixture	Bottle Mixture
		%	%	%
Adult	Excellent	33.0	34.9	50.0
	Good	51.0	44.9	36.1
	Poor	16.0	20.2	13.9
Juvenile	Excellent	15.8	15.5	36.0
	Good	55.6	49.3	36.0
	Poor	28.6	35.2	28.0

At the Mason Clinic in Seattle during 1946, Palmer[29] reported 236 patients seen for the first time. The average age was 49.8 years, and the average age at onset 44.2 years. Among the new adult patients degenerative diseases were very common. Thus, 41 per cent had hypertensive or arteriosclerotic heart disease, whereas of 429 diabetic patients admitted to the hospital, including the 236 new cases in the outpatient department, hypertensive and arteriosclerotic heart disease was present in 61.6 per cent. There was 1 death from diabetic coma among the 13 cases of acidosis treated, and of the 13 diabetic patients who were pregnant, 8 were delivered by cesarean section between the thirty-fifth and thirty-eighth weeks, resulting in 8 living children; in the remaining 5 cases, 3 infants were delivered spontaneously, 1 was stillborn and the other 2 died during the neonatal period. There was a miscarriage at thirteen weeks and a therapeutic abortion at five months because of the presence of uremia in the mother. Of the 2813 patients with diabetes followed at the Mason Clinic since 1917, 42 are known to have died during 1946, the average age at death being 60.6 years and the duration of diabetes being 13.1 years. Coronary thrombosis was responsible for 11 deaths, carcinoma for 7, cerebral thrombosis or hemorrhage for 6, diabetic coma for 4, and congestive heart failure due to hypertension or arteriosclerosis for 3, with intercapillary glomerulosclerosis, rheumatic heart disease, pyelonephritis and uremia, traumatic fracture of the spine, gangrene of the leg, tuberculosis of the lung, Addison's disease and xanthomatosis of the liver (primary) accounting for 1 each.

Only 3 juvenile diabetic patients were known to have died. Autopsy on 2 revealed extensive intercapillary glomerulosclerosis, and the clinical picture in the third led to the same diagnosis before he left the hospital to die elsewhere a few months later:

> Vascular degeneration, so evident . . . , remains the greatest challenge to the physician treating diabetes today. It is our incentive for insisting on rigid diabetic control in our patients.

In a subsequent article Palmer[30] reports favorably upon the use of insulin mixtures (Table 8). It is obvious that the ideal mixture has not been discovered, and in general it seems desirable for physicians to decide on the method of treatment of their patients with protamine-zinc insulin, separate injections of regular insulin or crystalline insulin and of protamine-zinc insulin, a mixture in the syringe, or premixed in a bottle, rather than to attempt the use of all four methods, which would almost certainly result in confusion. If physicians will only be patient for a year or two, undoubtedly new methods for the use of insulin will be found.

Campos and Molina,[31] in Buenos Aires, observed 25 consecutive cases of diabetes at all ages and reported on the fundus oculi. All these patients were poorly treated over a long period, and the most frequent combination was hypoalbuminemia, hypocholesterolemia and diabetic retinopathy. This combination appeared in 11 out of the 25 cases.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 34131

PRESENTATION OF CASE

A twenty-two-year-old linoleum layer was admitted to the hospital because of red urine.

Two months before admission, following a football game, he developed a sore throat accompanied by epistaxis and occasional biting of the tongue while asleep. Following this episode, which lasted an unstated period, he returned to work but was easily fatigued and slept a great deal. Three weeks before entry he again had severe epistaxes, sore throat and malaise. He had to leave his job on several occasions because of fatigue and drowsiness. During this period he developed red urine and was sent to another hospital, where he was catheterized because of inability to void. Thirty-two ounces of urine was obtained. While there he had a generalized convulsion. One day before transfer to this hospital he was again catheterized because of continuing retention. The face, neck and eyelids were edematous. He was treated with penicillin.

The patient had been an apparently normal child. At the age of six he developed enuresis. Repeated attempts to break him of this habit were unsuccessful. Urine was frequently analyzed but found to be normal. The enuresis persisted until two years before entry, when he married. Since then he had averted difficulty by getting up to void during the night. At the age of eight he had an appendectomy, and at ten the tonsils and adenoids were removed. At thirteen he was found to have an abdominal tumor. Examination revealed a distended bladder. A suprapubic cystotomy was performed, and no abnormality was found. The discharge diagnosis was "Distended bladder — retention of urine." About three years before entry he was rejected from the Army because of a "spina bifida." During the past two years he was noticed to limp to an increasing degree.

Physical examination revealed a very pale man in extremis. The breath was uremic. He had generalized twitching of the arms and a positive Chvostek sign. The skin was dry, and the neck veins were prominent. Examination of the fundi was negative. There was clotted blood in the nose. The apex of the heart was at the anterior axillary line, and there was a Grade III systolic murmur heard over the whole precordium but loudest at the pulmonic area. The chest was clear except for widely heard rhonchi. There was no ankle edema. There was an abscess in the right buttock. Some atrophy of the right calf muscles was present. There was bilateral pes-cavus deformity.

The temperature was 98.6°F., the pulse 90, and the respirations 14. The blood pressure was 180 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 2,800,000, with 10 gm. of hemoglobin, and a white-cell count of 25,000, with 88 per cent neutrophils and 12 per cent lymphocytes. The blood chloride was 98, and the carbon dioxide 9.1 milliequiv. per liter. The total protein was 6.8 gm. per 100 cc., and the nonprotein nitrogen 146 mg. The urine was red and had a specific gravity of 1.010. There was a +++ test for albumin and a + test for acetone. The sediment was loaded with red and white cells and there were rare casts.

One hour after admission the patient had a generalized convulsion, controlled by 1.5 gm. of calcium levulinate. He also received luminal, cedilanid and magnesium sulfate. He slowly received 1000 cc. of 5 per cent dextrose in water intravenously. He remained in a semicomatose state. An inlying catheter was inserted, and in one fifteen-hour period drained 1200 cc. of grossly bloody urine. The blood pressure, which had been running about 140 systolic, 70 diastolic, fell to 100 systolic, 55 diastolic, for no apparent reason, and he died thirty-six hours after admission. In the last fourteen hours of life he passed 10 cc. of urine.

Differential Diagnosis

Dr. Earle M. Chapman: This is indeed an interesting case and obviously is presented for the diagnosis of the type of kidney disease that led this man to die in rather classic uremia. He was in the hospital thirty-six hours so that very few studies were done.

But the review of the past history and the known facts presented here can lead to a diagnosis of a well recognized entity. I believe that he had a congenital defect — spina bifida — which eventually caused progressive changes in the spinal cord and what might be called a cord bladder. With this he had the other evidence of spina bifida — atrophy of the calf muscles and a bilateral pes-cavus deformity. Evidently through his early life this syndrome was not recognized. We cannot tell from the record, but I doubt it, because if it had been recognized, the patient would certainly not have been subjected to a suprapubic cystotomy unless a congenital valvular deformity, either in the neck of the bladder or in the urethra, was being sought. That this was not an acute process such as acute glomerulonephritis or acute pyelonephritis is indicated by the fact that he had evidence of chronic renal disease. In other words, the heart was enlarged, and he had hypertension, anemia and a fixation of the specific gravity of the urine at 1.010. All these findings indicate the long duration of the disease.

There is one note in the record that I take exception to — that after admission to the hospital an inlying catheter was inserted and in one fifteen-minute period 1200 cc. of grossly bloody urine was drained; the blood pressure, which had been running about 140 systolic, 70 diastolic, fell to 100 systolic, 55 diastolic for "no apparent reason." It has been the practice of the Genitourinary Service here that patients with chronic, long-standing obstruction to urinary outflow should not be decompressed rapidly, since removal of large quantities of urine in a short time leads to shock, fall of blood pressure and perhaps anuria. I think this is an example of such a reaction in this patient.

I can add little else. This is a recognized entity, although one has difficulty in finding a clear-cut description of it in textbooks. If the urinary tract had been studied and retrograde pyelograms done, which I judge were not since they have not been mentioned, the examinations would have shown a chronic atonic bladder, hydroureter and hydronephrosis. In this condition the kidneys end up with thin shells of cortex, — usually with some pyelonephritis, — but in this case there was very little evidence of pyelonephritis.

In conclusion, I would say that this man had spina bifida, cord bladder and the other evidence of central-nervous-system damage, and that with this he had an atonic, large bladder, a hydroureter, back pressure on the kidneys and small, atrophic kidneys, with a narrow rim of cortical tissue, and that he finally died in uremia, which at the end, at least, was not aided by the sudden withdrawal of a large amount of urine from the bladder.

Dr. H. J. Kowalski: I should like to ask Dr. Chapman how he explains the fact that the urine had been normal for a number of years. The patient's mother was a nurse and she had taken frequent specimens to a hospital for analysis and they had been consistently normal. Although we believed that this was acute nephritis, there were several features about it that were somewhat confusing. One was the low specific gravity of the urine (1.010). The fact that he had passed bloody urine and had renal failure following a sore throat, with epistaxis, of course, favored acute nephritis. Also, he had a high white-cell count. The terminal event was scanty, bloody urine, which is frequently seen in the end stage of this kind of process. I did not believe that this man died in shock. The blood pressure remained fairly well sustained, the pulse was good, and there were no signs of sweating or evidence in the extremities suggesting shock.

Dr. Fletcher H. Colby: I should think it was unusual even in the terminal stages of the condition such as you describe to have so much hematuria unless associated with a severe, acute infectious process or some other disease in the kidney. It is true that sudden decompression is not desirable, but the record says fifteen hours, not fifteen minutes.

Dr. Chapman: I misread the record. I shall have to retract that statement.

Dr. Colby: There is no adequate explanation for the copious hematuria?

Dr. Chapman: That is a puzzling point.

Dr. Allan M. Butler: One sees hematuria with pyelonephritis and pyuria.

Clinical Diagnoses

Acute glomerulonephritis.
Uremia.

Dr. Chapman's Diagnoses

Spina bifida.
Atonic bladder.
Hydroureters.
Atrophic kidneys.
Uremia.

Anatomical Diagnoses

Intradural lipoma of sacral canal.
Spina bifida occulta.
Dilatation and hypertrophy of bladder.
Hydroureters, bilateral.
Hydronephrosis, bilateral.
Pyelonephritis, chronic (with uremia).
Parathyroid hyperplasia, secondary.

Pathological Discussion

Dr. Benjamin Castleman: Autopsy showed what Dr. Chapman predicted. The bladder was tremendous, very thick and markedly trabeculated. There were numerous erosions of the mucosa. It is quite possible that the massive hematuria came from one or more of the mucosal erosions. Both ureters were markedly distended and thickened. There was a marked hydronephrosis, with only a shell of normal cortex remaining (Fig. 1). Not knowing about the spina bifida at that time, we immediately looked for a congenital valve in the urethra or some form of obstruction, but we were unable to find any. We then studied the history a bit more thoroughly and decided that the next thing to do was to examine the spinal cord and the spine. Dr. Kubik, will you tell us about that?

Figure 1. *Marked Hydronephrosis and Hydroureter. The bladder is markedly thickened and trabeculated. (Only a portion of the bladder is in the photograph, and it has been superimposed on the mid-portions of the ureters.)*

Dr. Charles S. Kubik: There was a spina bifida occulta involving the arch of the fifth lumbar vertebra and all of the sacrum.

Filling the sacral canal was an intradural mass of fat, or lipoma, measuring 5 cm. in length and from 2 to 3 cm. in diameter. This lay posterior to the spinal cord, which extended to the lower part of the sacral canal and was attached to the tumor by dense strands of fibrous tissue (Fig. 2). A condition such as this is not infrequently associated with spina bifida.

At birth in the normal person the lower end of the spinal cord occupies the lower part of the sacral canal. As growth takes place the spinal cord does not increase in length to the same extent as the vertebral column, so that in the adult the cord terminates at about the first lumbar vertebra and the vertebral canal below that is occupied by the spinal nerves of the cauda equina. In this case there was no cauda equina; the tip of the cord was anchored to the lower part of the sacral canal and held in that position as the vertebral column increased in length, with the result that the cord was stretched out and the course of the sacral and lower lumbar spinal nerves was actually reversed.

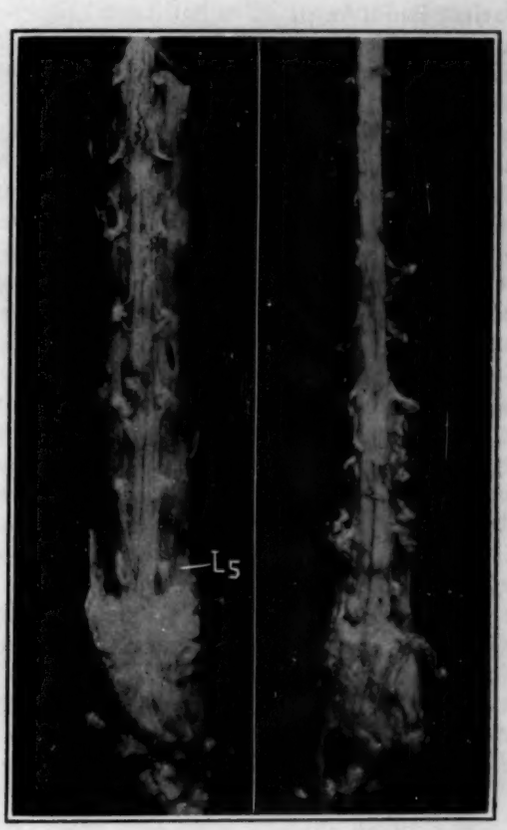

Figure 2. *Posterior* (A) *and Anterior* (B) *Views of the Lower Portion of the Spinal Cord and Intradural Lipoma of the Sacral Canal in a Case of Spina Bifida Occulta. The lowest visible spinal nerves in the posterior view* (A) *are the fifth lumbar. Note the upward course of these and other lumbar nerves.*

Dr. Butler: Was there any hydrocephalus?

Dr. Kubik: No — and no deformity of the cervical cord or cerebellum. In some cases of spina bifida the medulla and inferior poles of the cere-

bellum may be pulled down into the foramen magnum (Arnold–Chiari deformity), but that was not so in this case.

DR. J. B. AYER: It would be interesting to know whether the patient had other deformities. I suppose he was too sick to find out.

DR. KUBIK: He had clubfeet.

DR. AYER: Was he paralyzed?

DR. KUBIK: No, but there was some atrophy and the patient had a limp.

DR. AYER: That is consistent with other tumors of this character, with nerves running through the tumor without paralysis.

DR. KUBIK: Signs of pyramidal-tract disease sometimes develop at about the age of puberty, presumably because the cord is stretched as a result of active growth at that time.

DR. CASTLEMAN: Further evidence of long-standing renal impairment was the increased size of the parathyroid glands. They weighed over 400 mg. (about three times the normal weight) and microscopically showed secondary hyperplasia.

DR. CHAPMAN: What did you find in the kidneys?

DR. CASTLEMAN: An extensive, chronic, inflammatory process — pyelonephritis, such as one would expect, with a great deal of fibrosis and not much cellular infiltration, which may account for the absence of pyuria.

DR. KOWALSKI: Do you mean that the blood may have come from the bladder? The patient had hematuria three or four days before he entered the hospital.

DR. CASTLEMAN: I still believe it came from the bladder. There were no erosions in the ureter or pelves, but there were in the bladder.

CASE 34132

PRESENTATION OF CASE

An eight-week-old female infant was admitted to the hospital with a history of jaundice for two weeks and clay-colored stools for one week.

The child had been born three weeks prematurely following an uneventful pregnancy. Delivery was normal. The birth weight was 6 pounds, 12 ounces, and she had gained steadily until the day before admission to 10 pounds, 8 ounces. The patient's mother stated that jaundice was noticed for the first time two weeks before admission and then increased progressively. One week before admission the stools became clay colored instead of the usual yellow color, but there was no change in bowel frequency or stool consistence. During the night before admission the patient became irritable but continued to feed. On the morning of entry she vomited orange juice and ceased taking fluids, and the stools became loose, green, and frequent (twenty during the day). The urine was orange colored for the first time. In the eight hours previous to entry the patient had stiffness of the extremities accompanied by frothing at the mouth. There had been no cough, hematemesis, melena, bruising or head trauma.

Two siblings, five and two and a half years old, were well and had never had jaundice or convulsions.

Physical examination revealed an acutely ill, pallid, jaundiced child actively convulsing, with tonic upper extremities and clonic movements of the left leg. Anisocoria was present, the right pupil being larger than the left. The anterior fontanelle was tense. The liver edge was palpated four fingerbreadths below the right costal margin, and the spleen three fingerbreadths below the left costal margin. The abdomen felt full, and an umbilical hernia was present. There was no purpura, but the tourniquet test was positive.

The temperature was 99°F., the pulse 140, and the respirations 45.

Examination of the blood revealed a white-cell count of 20,000, with 46 per cent neutrophils, 33 per cent large lymphocytes, 9 per cent monocytes and 12 per cent blast forms. The hemoglobin was 8.5 gm. The urine was negative for urobilinogen and gave a + test for urobilin. A Harrison spot test was positive. A digital specimen of stool gave a ++ guaiac reaction. The bleeding time was 3½ minutes, and the clotting time, 2 or 3 minutes. The prothrombin time (after vitamin K therapy for twelve hours) was 13 seconds (normal, 16 seconds). The blood was Group O and Rh—. A van den Bergh reaction was 6.4 mg. per 100 cc. indirect and 1.8 mg. direct. The total protein was 6.4 gm. per 100 cc. Lumbar puncture showed an initial spinal-fluid pressure equivalent to 290 mm. of water; after removal of 4 cc. the pressure was equivalent to 110 mm. of water. The fluid was orange colored, with 20,000 red cells, 500 white cells per cubic millimeter and a +++ Pandy test. The total protein was 1040 gm. per 100 cc., and the sugar 165 mg. per 100 cc. A subdural tap on the left was negative; on the right 7 cc. of grossly bloody fluid under considerable pressure was removed and clotted on standing. An x-ray film of the chest was normal. A film of the abdomen showed a liver that appeared to be enlarged. The splenic outline was not definitely traced. The enlargement of the liver appeared to involve the left lobe.

The patient remained in coma, with many convulsive episodes. There was no remarkable response to repeated subdural taps or lumbar punctures. She was given blood transfusion, vitamin K and parenteral feedings. She expired at the end of the second hospital day after a few hours of hyperpyrexia.

DIFFERENTIAL DIAGNOSIS

DR. LEO B. BURGIN: In summary this eight-week-old infant had a disturbance involving two systems, the central nervous system and the biliary system.

I propose to deal with these separately and then, if possible, to relate them.

The conditions commonly causing jaundice during the early weeks of life are icterus neonatorum, congenital syphilis, erythroblastosis fetalis, sepsis and congenital malformations of the bile ducts — that is, atresia.

The history of increasing jaundice, clay-colored stools and orange-colored urine suggests a regurgitation or obstructive jaundice. Bile was found in the urine. Urobilinogen was absent.

Icterus neonatorum is generally considered to be a hemolytic or retention type of jaundice. It occurs in the first week of life. It would hardly be expected to continue as long as eight weeks, nor would its appearance be delayed until six weeks.

Syphilis does not seem likely. The family history was negative. There was no history of snuffles, rash or marked anemia, with or without an erythroblastic picture. Moreover, this baby thrived exceedingly well up to the time of admission. The hepatosplenomegaly and jaundice are consistent, but that is all.

Against erythroblastosis is the fact that the patient was Rh—. The jaundice appeared six weeks after delivery, and there were not the profound anemia and excessive numbers of erythroblasts usually found in the blood smear.

Sepsis with hemolysis might produce this picture. There is, however, no report of fever, although it is possible for infants to have overwhelming sepsis without fever. The elevated white-cell count may have been partially due to dehydration. There does not appear to have been a primary focus for infection unless we consider the diarrhea, which occurred terminally, however, some two weeks after the onset of the jaundice. Finally, the jaundice for the most part was obstructive although there is some evidence of a retention jaundice in the elevated indirect van den Bergh reaction. All in all, the course and history are against sepsis.

We come then to congenital atresia of the bile ducts. In this disorder, jaundice does not appear immediately. There is apt to be a period of two or three weeks before it is noted. In this case, however, jaundice did not appear until the child was six weeks old. It is possible that a slight degree of jaundice went unnoticed for a week or two earlier. Usually clay-colored stools are present from birth, but they may be tinged slightly with bile-stained mucous cells from time to time. Generally, these infants thrive quite well despite the absence of bile for digestion. Certainly, this child did quite well nutritionally almost to the day of death. In considering this diagnosis, I am disturbed by the high level of the indirect van den Bergh reaction. I can only explain it by suggesting that with increasing biliary obstruction the liver cells became functionally damaged and consequently unable to handle the normal daily destruction of red cells.

One other condition that I should like to mention is biliary obstruction from inspissated bile. The only difference from atresia is intermittency of the jaundice. We might infer this from the lack of history of clay-colored stools at the onset.

As for the central-nervous-system disturbance, the evidence presented points to subarachnoid hemorrhage as well as subdural hemorrhage. The presence of fresh red cells, increased protein in the lumbar tap and the history and findings of active convulsions suggest that this bleeding was recent. The most common cause of such bleeding is trauma, of which there was no history. It is possible that this bleeding might have occurred as a result of convulsions primarily due to the subdural hematoma, which was proved by tap.

Subdural hematomas are not uncommon in infancy. Trauma, not necessarily obvious at the time of delivery, may be responsible. The symptoms of increased pressure arise as the red cells in the hematoma disintegrate and hemoglobin and protein pass into the serum, producing a hypertonic fluid with subsequent increase in the size of the mass. The blood obtained from the tap clotted on standing. This suggests recent bleeding. Other causes for both sources of bleeding at this age are scurvy and hemorrhagic tendencies. There was no history of vitamin C intake, and I doubt whether eight weeks is sufficient to produce scorbutic symptoms. There was nothing in the blood picture to suggest purpura, leukemia or other blood dyscrasia. The prothrombin time was normal, but this was after vitamin K administration. We know that the patient had obstructive jaundice. With this disorder bleeding tendencies are not uncommon, and I believe that the subdural and subarachnoid hemorrhages were due to vitamin K deficiency secondary to obstructive jaundice.

Despite the delay in onset of jaundice and in the appearance of clay-colored stools, I believe this infant was suffering from congenital atresia of the bile ducts, subdural hematoma and subarachnoid hemorrhage secondary to liver damage.

There were some x-ray films that I should like to see.

Dr. Stanley M. Wyman: The liver seems a little large. The spleen cannot be traced accurately. I am not too impressed by the abnormal contour of the liver. The lung fields are clear, and the heart is not remarkable.

Dr. Burgin: I supposed, when I read about the enlargement of the left lobe of the liver, that possibly one hepatic duct closed later than the other hepatic duct, which might account for the greater enlargement on one side of the liver than the other. But I am not sure that that is a good explanation.

Dr. Allan M. Butler: I think the history as given omits the fact that a blood culture was taken and found to be negative.

DR. BURGIN: The question of the positive guaiac test in the stools could be explained either by the bleeding tendency or more likely by the fact that the child passed many stools, a total of twenty in one day, and that would be enough to irritate the rectum sufficiently to give a positive guaiac reaction.

DR. NATHAN B. TALBOT: Under the heading of congenital obliteration of the bile ducts, did you have in mind reduplication cysts or other conditions of that nature?

DR. BURGIN: No; just the ducts themselves — the hepatic, cystic and common ducts. I do not see how one can differentiate until operation.

DR. BUTLER: If the history is correct as given, it suggests that the baby was having normal-colored stools up to one week before admission, which would be odd for congenital atresia of the bile duct, and I think that makes one wonder about infection, inspissated bile and also pressure on the ducts, and lymph nodes.

DR. BURGIN: The child thrived well during the jaundice, and, if the illness had been due to sepsis, she would not have thrived so well. When jaundice is due to atresia of the bile ducts or inspissated bile, these children characteristically do quite well over a great number of months.

DR. TRACY B. MALLORY: We have only the mother's story for the color of the stools. It is not necessarily a reliable observation.

DR. TALBOT: Do we have any information about the platelets?

DR. GERTRUD C. REYERSBACH: They were normal.

CLINICAL DIAGNOSES

Subarachnoid bleeding.
Neuroblastoma?

DR. BURGIN'S DIAGNOSES

Congenital atresia of bile ducts.
Subdural hematoma and subarachnoid hemorrhage, secondary to liver damage.

ANATOMICAL DIAGNOSES

Congenital atresia of hepatic and cystic ducts.
Obstructive biliary cirrhosis.
Subdural hematoma, recent, right.
Intracerebral and subarachnoid hemorrhage.
Duodenal ulcers, multiple, acute.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The autopsy bore out Dr. Burgin's prediction. We found a gall bladder that contained only mucoid fluid with no trace of bile pigment. The cystic duct was a completely lumenless cord. The hepatic duct, which we could trace only a short distance and not all the way up to the liver, also appeared lumenless. The liver was symmetrically enlarged, deeply bile stained from stasis and a little granular. Microscopically it showed a moderate grade of biliary cirrhosis, which one expects to find in this condition. The central nervous system showed a large, subdural hematoma, and also a small intracerebral hemorrhage, which was the source of the subarachnoid hemorrhage. The surprising finding of the autopsy was multiple, acute ulcers in the duodenum, which may have had something to do with the positive guaiac reaction in the stool and reminds one of Dr. Cushing's description of peptic ulceration in association with a variety of cerebral lesions.

DR. CHESTER M. JONES: I should like to disagree with one statement that Dr. Burgin made: that if the stools were yellow colored, it might have been due to bile-stained mucus in the intestinal tract. I doubt very much if that is a valid explanation. If there is no bile coming through, how is the mucosa going to be bile-stained?

DR. BURGIN: Ladd and Gross* explain it, I believe, on the basis that all tissues are heavily bile stained in this condition and that the mucosa of the gastrointestinal tract also becomes stained.

DR. MALLORY: Some pigmentation might be the result of desquamation of bile-stained mucosal cells.

DR. TALBOT: I think that Dr. Burgin is right. Clinically, in marked jaundice of long standing, with atresia of the bile ducts, bile color appears in the stools coming through the intestinal mucosa rather than the liver.

DR. JONES: Perhaps desquamation itself.

DR. MALLORY: There was a long period before the jaundice was noted, and we were particularly anxious to rule out any possibility of a secondary atresia of the bile ducts, but we could find no inflammatory process around them. I think all the findings are very strongly in favor of congenital atresia.

DR. BUTLER: Do I notice in looking at the x-ray films from this distance that there is considerable osteoporosis that may be associated with long-standing liver disease?

DR. WYMAN: It is not very impressive to me. There might be slight osteoporosis.

DR. MALLORY: That also occurs with biliary fistulas rather more strikingly than with obstructive jaundice. The child did have a considerable degree of persistent hematopoietic activity in the liver and spleen but not enough to warrant a diagnosis of erythroblastosis.

*Ladd, W. E., and Gross, R. E. *Abdominal Surgery of Infancy and Childhood.* 455 pp. Philadelphia and London: W. B. Saunders Co., 1941. P. 260.

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THREATENED CURTAILMENT OF STATE LABORATORY SERVICES

COMMUNICATIONS published elsewhere in this issue of the *Journal* from Dr. Vlado A. Getting, commissioner of Public Health of the Commonwealth, and Dr. Louis K. Diamond, director of the Blood Grouping Laboratory of Boston, call attention to a serious situation. Unless additional funds necessary to meet greatly increased operating costs are provided by the Legislature, certain vital laboratory services must be curtailed.

One of these services is the Rh typing and grouping of bloods from pregnant women. The other is the diagnostic testing for virus diseases that has been carried on in co-operation with the Virus Laboratory of Harvard Medical School.

Funds to carry on these services have been requested in the annual budget of the Department of Public Health for two years, and nothing has been forthcoming. During these years the Blood Grouping Laboratory has come to the rescue, supplying approximately $20,000 from its own research funds. This support cannot and should not be continued for work that has now become a routine, important public-health service. If the Legislature cannot be led to appreciate the value of these measures their employment must cease.

Such a step would be intolerable. Public health must move forward, not backward. New tests provided by medical research should become available as they demonstrate their usefulness in saving lives. The Rh typing of the blood of 9000 women each year, provided for by funds from a private agency, is an example. Instead of the service being denied to this number it should be expanded to care for the 90,000 for whom it is applicable.

As with Rh typing and blood grouping in pregnancy, so also with the virus diseases that have been studied at Harvard Medical School. The implementing of public-health measures has been accepted as a function of the state. The state must be given the means of carrying them on.

The Department has used every resource at its command to emphasize to the appropriating agency the urgency of providing these invaluable services to the physicians of the Commonwealth. Unless outside aid is forthcoming it is likely that the plea for funds to provide them will be denied.

WHO

THE Interim Commission of the World Health Organization has issued a release giving in detail its activities during 1947. In this year it continued the greater part of the health services formerly rendered by the Health Organization of the League of Nations, the Office International d'Hygiène Publique and the Health Division of UNRRA.

One of the emergency services performed by the Interim Commission consisted of aiding the Egyptian Government in fighting the epidemic of cholera that scourged that country in the fall. During the course of this epidemic nearly 3,700,000 cc. of cholera vac-

cine was supplied to the stricken country, in addition to 32 tons of medical supplies and equipment.

The various activities of this organization make up a considerable list. The technical health assistance that had been given to fourteen devastated countries by UNRRA was assumed by WHO. Two hundred and twelve fellowships in public health were awarded to representatives of various governments for study outside their own countries. The WHO mission in China assumed emergency public-health work as well as the training of medical and technical personnel; in Greece a malaria-control problem that included the spraying or dusting with DDT of nearly 3500 malaria-ridden communities was inaugurated.

Ethiopia, whose technical experts were liquidated during the war with Italy, was assisted in developing basic programs of medical training and public-health administration; the Ethiopian Red Cross was revived and reorganized.

In addition a number of studies were made by committees of experts. The Committee for the Preparation of the Sixth Decennial Revision of the International Lists of Diseases and Causes of Death made improvements in the classification of vital statistics. The Expert Committee on Biological Standardization adopted international standards for vitamin E, heparin and penicillin, and other expert committees considered such subjects as malaria, tuberculosis and venereal disease; the unification of pharmacopeias; pilgrimages (such as the Mecca pilgrimage); quarantine; yellow fever; habit-forming drugs; and alcoholism.

Under the joint auspices of the Interim Commission and the Unitarian Service Committee a group of eight American and two Swiss physicians and surgeons visited Austria last summer on a teaching mission.

The World Health Organization will become a specialized agency of the United Nations when twenty-six States members of the UN have ratified its constitution. This has already been done by eighteen members. Within six months of final ratification the first World Health Assembly will convene, and the permanent machinery of the organization will be established.

NOW I LAY ME —

THOSE who received their medical training in a previous decade and have not since engaged in the practice of modern surgery may find themselves a little aghast at encountering postoperative patients walking about their rooms still reeking of ether. It is, however, in the tradition of today. We know that it is all for the best and that by these modern methods thromboses are prevented and embolic disturbances avoided. We have been made aware of the fact that despite their sojourn in a world of violence, most people still die in bed.

Those who indulge in a more placid form of medical practice than surgery have also become aware of the risks entailed in permitting patients to take too solidly to their beds. Levine[1] called attention to a few of them as long ago as September, 1944, when he showed that with bed rest a shift of edema may occur from the dependent parts of the anatomy to the patient's back; that recumbency increases the total blood volume, and adds the risk of hypostatic pneumonia; that in old men urinary retention may develop after recumbency has been instituted. In other words, there are dangers attendant upon bed rest besides that of pulmonary embolism.

Too often the colloquial expression "he took to his bed" implies a grim finality — a failure to rise again from the horizontal position.

Asher[2] carries the point still farther, expressing our old, innocent, somewhat naïve attitude toward bed in a quotation from *Hymns Ancient and Modern*, No. 23, Verse 3, as follows:

> Teach me to live that I may dread
> The grave as little as my bed.

Perhaps this obsolete attitude toward recumbency was also represented by the famous bed of Ware, on which several scores of couples could lie in apparent comfort. Disraeli, we are told, when in doubt took to his bed — a plagiarism on Voltaire.

Dr. Asher lists the strain of an overaddiction to recumbency on the respiratory system, the blood vessels, the skin, the muscles and joints, the bones, the renal tract, the alimentary tract, the nervous system and the mind:

Look at a patient lying long in bed. What a pathetic picture he makes! The blood clotting in his veins, the lime draining from his bones, the scybala stacking up in his colon, the flesh rotting from his seat, the urine leaking from his distended bladder, and the spirit evaporating from his soul.

The picture is overdrawn, he admits. Bed has its uses even in sickness, although the cardiac patient is often better off in a chair and all patients need exercise as soon as they are able to take it. It is moderation that Dr. Asher urges and that he implies in his final poetic outburst:

Teach us to live that we may dread
Unnecessary time in bed.
Get people up and we may save
Our patients from an early grave.

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1. Levine, S. A. Some harmful effects of recumbency in the treatment of heart disease. *J. A. M. A.* **126**:80-84, 1944.
2. Asher, R. A. J. Dangers of going to bed. *Brit. M. J.* **2**:967, 1947.

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S REPORT COVERING REFUND DISTRIBUTION

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to district societies for 1948.

The Council voted to distribute the sum of $8000.00 to district societies. The total number of payments of annual dues received by the Treasurer by March 1, to be counted for the refund, was 4541. Therefore, the refund to the district societies for each paid fellow is $1.76.

The following table gives the number of payments, as of March 1, and the refund to each district as of March 12:

District	Number Reported Paid	Refund
Barnstable	39	$68.65
Berkshire	122	214.72
Bristol North	58	102.68
Bristol South	183	322.84
Essex North	180	317.01
Essex South	252	444.02
Franklin	40	70.40
Hampden	287	505.68
Hampshire	61	107.36
Middlesex East	137	241.38
Middlesex North	125	220.36
Middlesex South	937	1,650.06
Norfolk	828	1,459.02
Norfolk South	148	260.69
Plymouth	135	238.03
Suffolk	549	967.01
Worcester	374	658.69
Worcester North	86	151.40
	4,541	$8,000.00

In 1947, for comparison, the total number of payments for the refund was 4527.

Eliot Hubbard, Jr., M.D., *Treasurer*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1948

Résumé

Disease	February 1948	February 1947	Seven-Year Median
Chancroid	4	2	1*
Chicken pox	1,839	2,542	1,340
Diphtheria	20	57	14
Dog bite	614	564	511
Dysentery, bacillary	11	13	9
German measles	78	101	188
Gonorrhea	186	346	345
Granuloma inguinale	0	1	0*
Lymphogranuloma venereum	2	2	1*
Malaria	3	8	8
Measles	2,092	2,021	1,877
Meningitis, meningococcal	11	7	19
Meningitis, Pfeiffer-bacillus	1	5	2
Meningitis, pneumococcal	2	6	5†
Meningitis, staphylococcal	0	1	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	2	1	0†
Meningitis, undetermined	3	6	5†
Mumps	1,559	668	1,091
Pneumonia, lobar	134	128	323
Poliomyelitis	2	0	0
Salmonellosis	5	5	4
Scarlet fever	433	627	1,201
Syphilis	198	271	363
Tuberculosis, pulmonary	218	189	192
Tuberculosis, other forms	11	13	14
Typhoid fever	1	0	2
Undulant fever	5	4	1
Whooping cough	294	620	620

*Four-year median.
†Six-year median.

Comment

Chicken pox, diphtheria, bacillary dysentery, measles, mumps, poliomyelitis and undulant fever are above the seven-year median for these diseases.

German measles, lobar pneumonia, scarlet fever and whooping cough are below the seven-year median.

Chicken pox is at the third highest prevalence for the month, the total cases having been exceeded only in 1944 and 1947.

Mumps is epidemic in Greater Metropolitan Boston and the northeastern part of the State as far as the New Hampshire line.

For the second consecutive month, scarlet fever is at the lowest level since 1906.

Whooping cough is at the lowest prevalence for February since 1917.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Belmont, 1; Boston, 6; Cambridge, 1; Everett, 1; Revere, 4; Somerville, 1; Springfield, 2; Wayland, 1; Winchester, 3; total, 20.

Dysentery, bacillary, was reported from: Worcester, 11; total, 11.

Encephalitis, infectious, was reported from: Quincy, 1; total, 1.

Malaria was reported from: Malden, 1; Reading, 1; Stoneham, 1; total, 3.

Meningitis, meningococcal, was reported from: Everett, 1; Fall River, 1; Lexington, 4; Malden, 1; Medford, 1; Millville, 1; Nahant, 1; Worcester, 1; total, 11.

Meningitis, Pfeiffer-bacillus, was reported from: Worcester, 1; total, 1.

Meningitis, pneumococcal, was reported from: Lowell, 1; Weston, 1; total, 2.

Meningitis, other forms, was reported from: Arlington, 1; Quincy, 1; total, 2.

Meningitis, undetermined, was reported from: Mansfield, 1; North Attleboro, 1; Worcester, 1; total, 3.

Poliomyelitis was reported from: Newton, 1; Worcester, 1; total, 2.

Salmonellosis was reported from: Brockton, 1; Everett, 1; Malden, 1; Melrose, 1; Newton, 1; total, 5.

Septic sore throat was reported from: Boston, 5; Brookline, 1; Falmouth, 1; Greenfield, 1; Upton, 1; total, 9.

Typhoid fever was reported from: Boston, 1; total, 1.

Undulant fever was reported from: Alford, 2; Bridgewater, 1; Gloucester, 1; Great Barrington, 1; total, 5.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The April schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Clinic	Date	Clinic Consultant
Lowell	April 2	Albert H. Brewster
Salem	April 5	Paul W. Hugenberger
Haverhill	April 7	William T. Green
Brockton	April 8	George W. Van Gorder
Greenfield	April 12	Charles L. Sturdevant
Gardner	April 13	Carter R. Rowe
Worcester	April 16	John W. O'Meara
Springfield	April 20	Garry deN. Hough, Jr.
Pittsfield	April 21	Frank A. Slowick
Hyannis	April 22	Paul L. Norton
Fall River	April 26	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

BLOOD GROUPING FACILITIES IN JEOPARDY

To the Editor: The following letter from Commissioner Vlado A. Getting discloses a situation that is distressing to many of us who appreciate the importance of the laboratory services offered by the Massachusetts Department of Public Health. It will be even more distressing when physicians and patients throughout the Commonwealth realize that this important assistance can no longer be obtained.

When the Executive Committee of the Blood Grouping Laboratory appropriated the money, two years in succession, to enable the state laboratory to perform Rh testing and blood grouping on blood samples submitted by physicians, particularly in prenatal cases, it was our desire to explore the usefulness of such testing as a public-health measure and to find out how many doctors would avail themselves of this free testing for the benefit of their patients. Scientifically, there can be no question that Rh typing and blood grouping are important, not only to the general public but more particularly to women during gestation. By knowing the blood group and Rh type, the physician can protect his patient against the hazards of emergency need for transfusion, which occurs suddenly as a complication of pregnancy from time to time, and can protect the infant, in certain cases, by helping establish promptly the diagnosis of erythroblastosis fetalis in the newborn and by providing immediate treatment. That this service by the state laboratory has been most useful is proved by the large number of doctors who have availed themselves of it, and by the fact that more than 1000 cases per month are now being tested. Certainly the peak has not been reached, and eventually it is quite possible that five or six times the present number of specimens would be sent to the State Laboratory if this work were permitted to continue. Unfortunately, the Blood Grouping Laboratory cannot continue to support from its research funds what is essentially a routine procedure, no matter how important this is as a public-health measure. It seems a pity, therefore, that this work should be allowed to lapse merely because its great value is not recognized by a committee of laymen.

I trust that this correspondence will help bring a distressing situation to the attention of physicians of the Commonwealth who recognize the need for this protective laboratory work, and that these physicians and their patients who have benefited will call the attention of their legislators to the error that will be made if the services of the state laboratory are curtailed in this respect.

Dr. Louis K. Diamond
Blood Grouping Laboratory
Children's Hospital
300 Longwood Avenue
Boston, Massachusetts

Dear Dr. Diamond:

I am writing to inquire about the possibility of the continuation of a grant from your organization to provide Rh typing and blood grouping of bloods from pregnant women.

As you know, last year and this, the Department requested funds to carry on this service in its budget. The funds were not provided for the current year, and the item was not included in the Governor's budget, which was presented to the Legislature in January.

I had an opportunity to present this matter once more to the Ways and Means Committee a few days ago. I shall not know until the budget is passed whether further consideration will be given to this request, but because of the extraordinary demands being made upon the Legislature this year, it is altogether likely that the funds needed for this work will not be provided.

As you know, we were able to carry out over 9000 tests on pregnant women for physicians of the Commonwealth during the last twelve months. It will be quite a blow to the Department if it becomes necessary to curtail this service.

We are in essentially the same situation in diagnostic tests for virus diseases, which have been carried out in co-operation with the Virus Laboratory of the Harvard Medical School. Sufficient funds for the continuation of this work were not included in the expense item of the Division of Communicable Diseases in the budget submitted to the Legislature.

May I please hear from you regarding the possibility of continuing this service under a grant from your organization.

Vlado A. Getting
Commissioner

Commonwealth of Massachusetts
Department of Public Health
State House
Boston

Louis K. Diamond, M.D.
Director

Blood Grouping Laboratory
300 Longwood Avenue
Boston

FURTHER COMMENT ON "UNNECESSARY OPERATIONS"

To the Editor: I wish to subscribe to the comments made in the editorial "Unnecessary Operations," which appeared in the March 4 issue of the *Journal*. I imagine this editorial was written by one of your associates who is extremely well versed and qualified to comment on this subject. I simply wish to agree with statements and to add a comment or two based on my own experience.

The statistical improvement in mortality rates from appendicitis is most gratifying to everyone. The reasons for this improvement are, in my opinion, the result of better management of the individual patient and to a lesser extent better operative technic, and antibiotics and chemotherapy. It is not attributable to earlier or more accurate diagnoses so far as my observations indicate. Admissions to a specialized hospital for the young seem very much the same as they did fifteen years ago so far as appendiceal peritonitis is concerned. There has been an opportunity to observe admissions to two surburban and one Government hospital where the same situation obtains. My own experience in the past two years is similar.

I believe, therefore, that the article that inspired the editorial is capable of doing a great deal of harm. Relatively speaking, appendicitis is not a rare disease in childhood.

Prompt recognition of the disease is not common. Appendicitis is a diagnosis to be considered seriously when abdominal pain is a presenting symptom, and presence of localized tenderness, with or without supporting findings, is of the greatest importance. Home observation of such

patients is often unsatisfactory owing to environmental conditions including the emotional status of the family. Frequently, observations and laboratory support may not be feasible in the home. The proper place for a patient with an abdominal pain and without a definite diagnosis is in a hospital that is properly equipped and staffed.

HENRY W. HUDSON, JR., M.D.

1101 Beacon Street
Brookline

NO MORE SPECIALISTS NEEDED

To the Editor: In the editorial entitled "The Second Age of Dependency," which appeared in the March 4 issue of the *Journal*, the last paragraph reads: "Perhaps we may need to add yet another specialty that will determine degrees of health rather than of disease, whose representatives will endeavor to preserve, extend and enhance the physical and mental well-being of the healthy and labor to keep apart the fields of the pediatrician and the geriatrist."

This sentence brings up a rather important point, which needs certain clarification. The point is that a new, separate field of specialization may be needed. The clarification is that such a field properly should exist so far as the research aspect is concerned, but it should *not* exist so far as the aspects of teaching or clinical practice are concerned. This is neither an argument simply of the old familiar general practitioner vs. specialist variety nor is it one of semantics.

The opinion of the slowly growing but still small number of physicians who have been interested in this field for many years (of whom I happen to be one) is somewhat as follows. The fundamental approach to a student's study of medicine should be through a study of man as a whole, not through unrelated study of his various anatomic, physiologic and psychologic parts. Secondly, the anthropologic, sociologic and general environmental aspects of man's existence should be given more consideration in the teaching given by medical-school staffs. Thirdly, the concept that an adequate understanding of man can be obtained through a consideration only of his symptoms or his disease is basically fallacious and should be replaced by a primary approach to man through consideration of him in his healthy state, the secondary approach being through disease. Finally, these suggested changes in the fundamental approach to the study of medicine should become inherent in the approach of all teachers whatever specialty they may represent and should not become the province of a newly created group of specialists.

JOHN P. MONKS, M.D.

Harvard University
Department of Hygiene

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Studies from the Rockefeller Institute for Medical Research. Reprints. Volume 133. 8°, paper, 604 pp. New York: The Rockefeller Institute for Medical Research, 1947. $2.00.

This volume is made up of reprints of papers originally printed in various periodicals and here brought together for convenience in reference. They constitute the results of investigations conducted at the Rockefeller Institute and published in 1946.

A Handbook of Ocular Therapeutics. By the late Sanford R. Gifford, M.D., professor of ophthalmology, Northwestern University Medical School, Chicago. Revised by Derrick Vail, M.D., D.O. (Oxon.), professor of ophthalmology, Northwestern University Medical School, Chicago. Fourth edition. 8°, cloth, 336 pp., with 66 illustrations. Philadelphia: Lea and Febiger, 1947. $5.00.

Dr. Gifford died in 1944, and Dr. Vail assumed the task of revising this fourth edition of a standard textbook. There has been some revision to bring the text up to date. New material has been added on penicillin and the sulfonamides. The chapter on disorders of the muscular apparatus has been eliminated, since it was considered out of place in a book of this type. Selected references are appended to each chapter, and there is a good index. The book is well published in every way. Although it has passed through four editions there is nothing to indicate its publication history. This is to be deplored, for a book worthy of repeated editions should at least give the dates of the various editions on the back of the title page. The work is recommended for all medical libraries and should prove of value to specialists in the field of ophthalmology.

Internal Medicine in General Practice. By Robert P. McCombs, M.D., assistant professor of medicine and director of postgraduate teaching, Tufts College Medical School, and senior attending physician, Joseph H. Pratt Diagnostic Hospital, Boston. Second edition. 8°, cloth, 741 pp., with 122 illustrations. Philadelphia: W. B. Saunders Company, 1947. $8.00.

Dr. McCombs has thoroughly revised this new edition of his work first published in 1943 and has adhered to his original plan of providing a text in which basic principles of everyday problems in internal medicine are factually reviewed and controversial material omitted or strictly condensed. Special emphasis has been placed upon diseases in which errors in diagnosis and therapy commonly occur. Diagnostic and therapeutic methods most readily adaptable for use in general practice have been stressed. New chapters have been added on psychiatric disorders and on the common vascular disorders of the extremities. Chemotherapy has been completely rewritten to include the use and abuse of penicillin and streptomycin and their relation to the sulfonamides. New material includes lumbodorsal sympathectomy in hypertension, the rice diet in hypertension and certain kidney diseases, high-protein diets and protein hydrolysates in malnutrition, folic acid in macrocytic anemias and sprue, serum albumin in circulatory failure and nephrotic conditions, gamma globulins in measles and infectious hepatitis, chloroquine in malaria, para-aminobenzoic acid in rickettsial diseases, thiouracil in hyperthyroidism, estrogen therapy and castration in cancer of the prostate, benadryl and pyribenzamine in allergic disorders, cytochrome C in anoxic states, tridione in psychomotor disorders and heparin and dicumarol in vascular emergencies. A list of selected references is appended to each chapter, and there is a good index. The book is well published in every way and should be in all medical libraries and should prove valuable to practicing physicians.

An Introduction to Biochemistry. By William R. Fearon, M.A., Sc.D., M.B., fellow of Trinity College and professor of biochemistry, University of Dublin, fellow of the Royal Institute of Chemistry and member of the Royal Irish Academy. Third edition. 8°, cloth, 569 pp., illustrated. New York: Grune and Stratton, 1947. $6.00.

This third edition of a work first published in 1934 has been thoroughly revised and many new sections added. More emphasis has been placed on certain subjects of special interest in clinical medicine, including acid-base balance, animal calorimetry, carbon dioxide transport, energy transformation, blood chemistry, bone formation, food absorption and detoxication. A chapter on tissue chemistry has been added, and the chapter on nutrients has been rewritten. A good index completes the volume.

Surgery of the Ambulatory Patient. By L. Kraeer Ferguson, M.D., professor of surgery, Graduate School of the University of Pennsylvania, professor of surgery, Woman's Medical College of Pennsylvania, surgeon, Graduate Hospital of the University of Pennsylvania, Woman's Medical College Hospital, Philadelphia General Hospital and Doctors Hospital, and consulting surgeon, United States Naval Hospital. With a section on fractures by Louis Kaplan, M.D., associate in surgery, University of Pennsylvania, chief, Surgical Service II, Mt. Sinai Hospital, and in charge of the fracture division of the Surgical Out-Patient department, Hospital of the University of Pennsylvania. Second edition. 8°, cloth, 932 pp., with 645 illustrations. Philadelphia: J. B. Lippincott Company, 1947. $10.00.

Dr. Ferguson, in revising his standard office surgery, first published in 1942, has endeavored to bring up to date subjects in which definite progress has been made since the pub-

lication of the first edition. The work has been written for young surgeons and general practitioners for office use in the treatment of patients not necessitating hospitalization. Material has been added on penicillin and the use of the sulfonamides and on tendon suture, back lesions and varicose veins. The material is well organized, and a list of selected references is appended to each section. A good index concludes the volume. The book is well printed with a good type on coated paper. The use of filled paper makes the volume too heavy for its size. The printing of valuable illustrations on the lining of the front cover is bad practice and should be eliminated in succeeding editions. The work is recommended for all medical libraries and should prove valuable to physicians and surgeons. In passing it is worth noting that during the past few years the Lippincott Company has established a fine line of medical publications.

New and Nonofficial Remedies — 1947: Containing descriptions of the articles which stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1, 1947. Issued under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. 12°, cloth, 749 pp. Philadelphia: J. B. Lippincott Company, 1947. $3.00.

This new edition of a standard reference work has been printed on a heavier durable paper, and the color of the binding has been changed to red, resulting in a more distinctive volume. A chapter on unclassified therapeutic agents, including gold and iodine compounds for systemic use, has been added, and the descriptions of thirteen new preparations have been included in the text. They comprise the pertussis vaccines and combinations of pertussis and diphtheria and tetanus vaccines; benadryl hydrochloride elixir, the new histamine-antagonizing agent; furacin, a topical anti-infective agent; streptomycin; parenamine, a new casein hydrolysate; thiouracil; naphuride sodium, a new trypanocide; and tuamine, a new vasoconstrictor. The section devoted to the statement of the Council's rules has been amplified and indexed. The material on tests and standards has been brought together in the back of the volume, in a new section B, and printed in small type, too small for reading comfort. The book should be in all medical libraries and should prove valuable to all persons interested in the use, preparation and manufacture of drugs. The work is no longer published by the American Medical Association but has been transferred to a medical-book publisher.

Colloid Science: A symposium. 8°, cloth, 208 pp. Brooklyn: Chemical Publishing Company, Incorporated, 1947. $6.00.

This symposium is based on a postgraduate course sponsored by the Department of Colloid Science, Cambridge University, England. Eleven persons took part in the course, and their papers are contained in this volume. The book deals with "disperse systems" and interpretations of phenomena encountered in surface films and interfaces. The subjects covered include surface chemistry and colloids; thermodynamics; the study of macromolecules or polymers; emulsions in vivo; and the study of colloidal systems by x-ray analysis. The chapter on emulsions discusses fat metabolism at length. The volume is well published, but the price seems excessive.

Overcoming Stammering. By Charles Pellman. With a foreword by Frederick Martin, M.D., director of National Institute for Voice Disorders, Bristol, Rhode Island, and director of Speech Clinics, State Department of Education, Rhode Island. 8°, cloth, 160 pp. New York: The Beechhurst Press, 1947. $3.00.

Mr. Pellman, an experienced practicing speech correctionist, analyzes and evaluates current methods of speech correction and treatment. He presents a plan for speech correction of stammering and stuttering based upon the physiology of speech and proper mental hygiene, rather than on the functioning of the speech apparatus. His method may be used in the home by intelligent parents. The text ends with an autobiographic sketch of a stammerer by Aaaro Pellman. A list of books and an index concludes the volume. The book is well published. It is recommended for medical and educational libraries.

Symptoms and Signs in Clinical Medicine: An introduction to medical diagnosis. By E. Noble Chamberlain, M.D., M.Sc., lecturer in medicine, University of Liverpool, physician to out-patients, Royal Liverpool United Hospital, Royal Infirmary Branch, and visiting physician, Smithdown Road Hospital, Liverpool. Fourth edition. 8°, cloth, 463 pp., with 346 illustrations. Baltimore: Williams and Wilkins Company, 1947. $8.00.

First published in 1936, this manual primarily written for the medical student has passed through nine printings and four editions, testifying to its soundness and popularity. This edition has been thoroughly revised, and certain chapters have been largely rewritten, especially those on the nervous system. Material has been added throughout the text. The material is well organized, and the book well printed with a good clear type. Although of British origin the work should prove useful to students and physicians in the United States.

May's Manual of the Diseases of the Eye: For students and general practitioners. By Charles A. Perera, M.D., assistant clinical professor, College of Physicians and Surgeons, Columbia University, New York, and assistant attending ophthalmologist, Presbyterian Hospital, New York. Nineteenth edition. 12°, cloth, 521 pp., with 387 illustrations, including 32 plates and 93 colored figures. Baltimore: Williams and Wilkins Company, 1947. $4.00.

First published in 1900, this standard manual has enjoyed a great popularity over the ensuing forty-seven years. Since the publication of the eighteenth edition in 1943 Dr. May has died, and the work is now being carried on by Dr. Perera. Editions have been printed in Portuguese and Chinese since 1943, and nine editions in all have been published in Great Britain. The present edition has been thoroughly revised and brought up to date, and much material added, including penicillin therapy, the modern theory of color vision and its anomalies, thyrotropic and thyrotoxic exophthalmos, congenital cataract following maternal rubella, and ocular brucellosis. The book is well published and should prove useful to students and general practitioners.

Diseases Transmitted from Animals to Man. By Thomas G. Hull, Ph.D., director, The Scientific Exhibit, American Medical Association. Third edition. 8°, cloth, 571 pp., with 75 illustrations and 67 tables. Springfield, Illinois: Charles C Thomas, 1947. $10.50.

In this third edition of a standard reference work material has been added on the rickettsial and virus diseases, including new chapters on tsutsugamushi disease, Q fever, jungle yellow fever, lymphocytic choriomeningitis and milker's nodules. Other new chapters consider listerellosis and Haverhill fever. Practically the entire book has been rewritten or revised. A list of selected references is appended to each chapter. The type and printing are excellent, and wide margins are back again, resulting in good reading conditions. The weight of the volume might be reduced by the use of a nonfilled paper. The book is recommended for all medical and public-health libraries and as a reference work for physicians.

Rypins' Medical Licensure Examinations: Topical summaries, questions and answers. Under the editorial direction of Walter L. Bierring, M.D., M.R.C.P. Edin. (Hon.), secretary, Federation of State Medical Boards of the United States. Sixth edition. With the collaboration of a review panel. 8°, cloth. 690 pp. Philadelphia: J. B. Lippincott Company, 1947, $6.00.

This standard reference work, first published in 1933 and last revised in 1945, has again been revised to incorporate advances in knowledge occurring during the past two years. A chapter has been added on psychiatry. The book is well published, and it is a delight to find that it is printed on a good, light, soft paper. Although this increases the thickness of the volume in relation to the number of pages, it reduces the weight correspondingly and makes it easier to handle the volume. This reference book should be included in all medical libraries.

NOTICES

ANNOUNCEMENTS

Drs. Francis C. Hall and Theodore B. Bayles announce the removal of their offices to 1180 Beacon Street, Brookline, for the practice of internal medicine and rheumatic diseases.

Dr. Elliot L. Sagall announces the opening of an office for the practice of internal medicine at 171 Bay State Road, Boston.

Dr. George P. Sanborn, 384 Commonwealth Avenue, Boston, announces his retirement from the practice of medicine on February 20, 1948. His address will be Winterport, Maine.

Dr. Leslie H. Van Raalte announces the removal of his office to 68 Russell Park, Quincy.

TUFTS MEDICAL ALUMNI ASSOCIATION ANNUAL DINNER

The annual dinner meeting of Tufts Medical Alumni Association will be held at the Hotel Somerset, Boston, on Wednesday evening, April 7, at 6:30.

The guest speaker will be Admiral Luis de Florez, Sc.D., who will talk on "New Engineering Developments in the Science of Medicine."

Other speakers include Dr. Stanley H. Osborn, commissioner of health, Connecticut, and professor of public health, Yale University; Reverend Michael J. Ahern, S.J., director of seismology, Weston College; Dr. Frank R. Ober, president, Tufts Medical Alumni Association; and Dr. Bernard Appel, professor of dermatology, Tufts College Medical School. Dr. Leonard Carmichael, president of Tufts College, will discuss the progress of the medical school.

MASSACHUSETTS GENERAL HOSPITAL RESEARCH COUNCIL MEETING

A meeting of the Massachusetts General Hospital Research Council will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, on Thursday, April 8, at 4:30 p.m.

PROGRAM

Electrical Stimulation of the Orbital Surface of the Frontal Lobe and Frontal Lobotomy in Men: Their effect on blood pressure and respiration. Drs. W. P. Chapman, R. B. Livingston and K. Livingston.

Clinical and Laboratory Studies on Beryllium Toxicology. Drs. R. S. Greer, P. Nash and D. G. Freiman.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, April 13, at 8:00 p.m.

PROGRAM

The Uptake of Radioactive Phosphorus by Gastric Carcinoma.
Drs. J. Schulman, Jr., S. J. Gray and M. Falkenheim.

Relief of Anginal Pain by Carotid Sinus Stimulation.
Drs. W. P. Harvey and S. A. Levine.

The Pulmonary Capillary Pressure in Man.
Drs. H. K. Hellems, F. W. Haynes, J. F. Gowdey and L. Dexter.

Circulatory Dynamics in Pulmonary Vascular Disease.
Drs. J. W. Dow, J. L. Whittenberger, E. C. Eppinger and H. P. Brean.

The Use of Adrenocorticotropic Hormone in the Evaluation of Adrenal Cortical Reserve in Man.
Drs. P. H. Forsham, G. W. Thorn, L. Recant and A. G. Hills.

The Mechanism Involved in the Breakdown of Circulating Leukocytes.
Drs. P. Fremont-Smith and C. B. Favour.

Iron Transport.
Drs. C. E. Rath, Jr., C. A. Finch, J. G. Gibson, 2nd, and R. Fluharty.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheatre, White Building, Massachusetts General Hospital, on Tuesday, April 13, at 8 p.m. A scientific program entitled "Boston University Medical School Night" will be presented.

PROGRAM

Cardiac Irregularities under Cyclopropane Anesthesia: Studies on mechanism.
Drs. Frank Pettinga and J. W. Stutzman.

Respiratory Arrest Resulting From Hypoxia after Dibenamine.
Drs. Eben Dustin and George L. Maison.

Effect of Pentothal Sodium on Blood Gas Transport.
Drs. K. E. Penrod and A. H. Hegnauer.

Physicians and medical students are invited to attend.

NEW ENGLAND DERMATOLOGICAL SOCIETY

The regular annual meeting of the New England Dermatological Society will be held at the Skin Out-Patient Department of the Boston City Hospital on Wednesday, April 14, at 2:00 p.m.

These meetings are open only to members and invited guests.

AMERICAN SURGICAL ASSOCIATION

A meeting of the American Surgical Association will be held at the Chateau Frontenac, Quebec, on May 27, 28 and 29.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The thirteenth scientific session of the National Gastroenterological Association will be held at the Hotel Pennsylvania in New York City from June 7 to 10.

In response to popular request the program this year will again for the most part consist of symposiums, and there will be one panel discussion.

The program for the first three days, at the Hotel Pennsylvania, will consist of symposiums on gastroduodenal ulcer; ulcerative colitis; jaundice and metabolism, nutrition and allergy. The panel discussion, which will be followed by a question-and-answer period, will cover the topics of diabetic, tuberculous, psychosomatic and cardiac manifestations in gastrointestinal diseases.

The fourth day of the session will be devoted to clinics at co-operating hospitals in New York City.

Further details and a copy of the program may be obtained by application in writing to the Secretary, National Gastroenterological Association, 1819 Broadway, New York 23, New York.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Board of Examiners of the American College of Chest Physicians announces that the next oral and written examinations for fellowship will be held at Chicago on June 17. Candidates who would like to take the examinations for fellowship in the college should communicate with the Executive Secretary, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

The fourteenth annual meeting of the American College of Chest Physicians will be held at the Congress Hotel, Chicago, from June 17 to 20.

STUDENTS' INTERNATIONAL CLINICAL CONGRESS

The International Union of Students and the British Medical Students Association invite a delegation of fifteen medical students from the United States of America to a Students' International Clinical Congress of 200 delegates to be held in England from July 6 to 24. Lectures, seminars

and clinical teaching will be held in London, Oxford and Birmingham. Transportation and housing will be arranged at minimal expense. Further information may be obtained from Anna P. Cort, chairman, Committee on International Clinical Congress, AIMS, Boston University School of Medicine, 80 East Concord Street, Boston.

NATIONAL RESEARCH COUNCIL GRANTS FOR RESEARCH

The Committee on Human Reproduction of the National Research Council, acting for the National Committee on Maternal Health, Inc., announces that grants for research in the field of reproduction are available. Applications to become effective July 1, 1948, will be received until May 1, 1948; applications to become effective October 1, 1948, will be received until August 1, 1948.

The committee will consider support of biologic, clinical, economic, medical, psychologic and sociologic research dealing broadly with the field of human reproduction in general and with specific problems, including maternal and fetal physiology, the factors controlling conception, the physiology of fertilization and conception, and sterility. For the year 1948–1949, the committee will place specific emphasis upon investigations of the factors controlling conception, fertility and sterility, but other fields of endeavor will be supported if projects of special significance are presented. In subsequent years, changing emphasis may be anticipated.

The National Committee on Maternal Health has advised the National Research Council that it proposes to solicit funds to finance the program of research recommended by the Committee on Human Reproduction to an amount of approximately $200,000 for 1948–1949.

Communications regarding grants should be addressed to Committee on Human Reproduction, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

AMERICAN DERMATOLOGICAL ASSOCIATION

The annual meeting of the American Dermatological Association will be held in Coronado, California, from April 26 to 29 (secretary, Harry R. Foerster, M.D., 208 East Wisconsin Avenue, Milwaukee, Wisconsin).

AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

The annual meeting of the American Gastro-Enterological Association will be held in Atlantic City on April 30 and May 1 (secretary, Dwight L. Wilbur, M.D., 655 Sutter Street, San Francisco, California).

AMERICAN SOCIETY FOR CLINICAL INVESTIGATION

The annual meeting of the American Society for Clinical Investigation will be held in Atlantic City on May 3 (secretary, E. A. Stead, Jr., M.D., Duke Hospital, Durham, North Carolina).

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The annual meeting of the Association of Military Surgeons of the United States will be held in Atlantic City, New Jersey, on May 4 and 5 (secretary, James M. Phalen, M.D., Army Medical Museum, Washington 25, D. C.).

MEDICAL ASSOCIATION OF GEORGIA

The annual meeting of the Medical Association of Georgia will be held in Atlanta from April 27 to 30 (secretary, E. D. Shanks, M.D., 478 Peachtree Street, N. E., Atlanta 3, Georgia).

IOWA STATE MEDICAL SOCIETY

The annual meeting of the Iowa State Medical Society will be held in Des Moines from April 19 to 21 (secretary, John C. Parsons, M.D., 406 Sixth Avenue, Des Moines 9, Iowa).

MEDICAL AND CHIRURGICAL FACULTY OF MARYLAND

The annual meeting of the Medical and Chirurgical Faculty of Maryland will be held in Baltimore on April 27 and 28 (secretary, George H. Yeager, M.D., 1211 Cathedral Street, Baltimore 1, Maryland).

MEDICAL SOCIETY OF NEW JERSEY

The annual meeting of the Medical Society of New Jersey will be held in Atlantic City from April 26 to 29 (secretary, Earl L. Wood, M.D., 315 West State Street, Trenton 8, New Jersey).

OKLAHOMA STATE MEDICAL ASSOCIATION

The annual meeting of the Oklahoma State Medical Association will be held in Oklahoma City from April 18 to 22 (secretary, R. H. Graham, 210 Plaza Court Building, Oklahoma City 3, Oklahoma).

STATE MEDICAL ASSOCIATION OF TEXAS

The annual meeting of the State Medical Association of Texas will be held in Houston from April 26 to 29 (secretary, Holman Taylor, M.D., 1404 West El Paso Street, Ft. Worth 3, Texas).

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, April 1

Friday, April 2

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Monday, April 5

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Tuesday, April 6

*12:00 m. X-ray Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, April 7

*12:00 m. Grand Rounds and Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

6:30 p.m. Tufts Medical Alumni Association Annual Dinner. Hotel Somerset, Boston.

*Open to the medical profession.

March 28–April 4. American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston.

March 29. New England Heart Association. Page 419, issue of March 18.

March 30–April 1. American Association of Industrial Physicians and Surgeons. Page 419, issue of March 18.

April 7. Tufts Medical Alumni Association Annual Dinner. Page 455

April 7–9. American Laryngological, Rhinological and Otological Society. Page 419, issue of March 18.

April 7, 9, 14 and 16. American Trudeau Society. Page 240, issue of February 12.

April 8. Endometriosis. Dr. John Fallon. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 8. Massachusetts General Hospital Research Council Meeting. Page 455.

April 10. American Congress of Physical Medicine. Page 344, issue of March 4.

(*Notices concluded on page xix*)